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Clinical Presentation and Management of Paget's Disease of Bone

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A thesis submitted to the University of Edinburgh in fulfilment of the requirements for the degree of Doctor of Medicine (MD)

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This thesis is dedicated to my wife, Lay Ean and our son, Darren.

Declarations

I hereby declare that this thesis has been written by myself and has not been accepted in any previous application for a degree. All work described in this thesis has been carried out by myself, except where specifically acknowledged. All sources of information used in this thesis have been included in the references

Adrian Tan

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Abbreviations

ALP	Alkaline Phosphatase
ANOVA	Anaysis of Variance
ATP	Adenosine Triphosphate
CI	Confidence Interval
CNS	Central Nervous System
CSF	Colony Stimulating Factor
CTx	C-terminal telopeptide
DC-STAMP	Dendritic cell-specific transmembrane protein
DNA	Deoxyribonucleic acid
ENT	Ear Nose & Throat
ESH	Expansile Skeletal Hypophosphatasia
EQ-5D	EuroQOL five dimensions questionnaire
FEO	Familial Expansile Osteolysis
FPP	Farnesyl diphosphate
GRADE	Grading of Recommendations Assessment, Development and Evaluation
GTP	Guanosine Triphosphate
GTPase	Guanosine Triphosphate hydrolase enzyme
HAQ	Health Assessment Questionnaire
IBMPFD	Inclusion body myopathy, Paget's disease and frontal-temporal dementia
IPP	Isopentenyl diphosphate
IPTW	Inverse Probability of Treatment Weighting
ITT	Intention-to-treat
LRP	Lipoprotein Receptor-related Protein

M-CSF	Macrophage-Colony Stimulating Factor
MD	Mean Differences
MOS	Medical Outcome Study
NFκB	Nuclear factor kappa B
NNH	Number Needed to Harm
NNT	Number needed to treat
NSAID	Non-steroidal anti-inflammatory drugs
NTx	N-terminal telopeptide
OPG	Osteoprotogerin
OPTN	Optineurin
OR	Odds Ratio
P1NP	Procollagen Type 1 Amino-terminal propeptide
PDB	Paget's disease of Bone
PML	Promyelocytic leukaemia
PRISM	Paget's disease Randomised trial of Intensive versus Symptomatic Management
PRISM-EZ	Paget's disease Randomised trial of Intensive versus Symptomatic-Extension with Zoledronate
QoL	Quality of Life
RANK	Receptor activator of nuclear factor kappa-B
RANK-L	Receptor activator of nuclear factor kappa-B Ligand
RCT	Randomised Controlled Trials
RD	Risk Differences
RIN3	Rab and Ras Interactor 3
ROR	Receptor tyrosine kinase-like Orphan Receptor
RR	Risk Ratio
SF36	Short Form Survey 36-Item
SMD	Standardised Mean Difference

SQSTM1	Sequestosome 1
TM7SF4	Transmembrane 7 superfamily member 4
TNFRSF11a	Tumour Necrosis Factor Receptor Superfamily, member 11a
TNFRSF11b	Tumour Necrosis Factor Receptor Superfamily, member 11b
UB	Ubiquitin
UBA Domain	Ubiquitin Associated Domain
UK	United Kingdom
USA	United States of America
VCP	Valosin Containing Protein
ZIPP	Zoledronate in the Prevention of Paget's

Lay Summary

Paget's Disease of Bone (PDB) is the second most common metabolic bone disease. The majority of patients with PDB are often asymptomatic and many are identified incidentally from tests performed for a different and often unrelated reason. Of those who do come to medical attention, bone pain is the commonest symptom followed by deformity, deafness and fracture. These findings have consistently been reported over the years although it is interesting to note that studies undertaken more recently, examining the mode of presentation of PDB have uncovered a higher rate of bone pain and a lower rate of fracture compared to older studies. The exact reasons for these changes are uncertain.

Serum Alkaline Phosphatase (ALP) levels are often elevated in patients with PDB. The presence of underlying active metabolic bone activity is thought to be the reason for this elevation. Bisphosphonate therapy has been shown to be effective in reducing, and in many cases normalising ALP levels, and is useful in alleviating bone pain secondary to PDB. The use of repeated courses of bisphosphonates with the aim of normalising ALP levels however, has not been shown to result in better outcomes, and conversely, has been linked with higher rates of fracture and requirement for orthopaedic surgery. The use of bisphosphonates should hence be tailored to the patient's symptoms rather than to suppress serum ALP levels

Abstract

PDB is the second most common metabolic bone disease characterised by increased but disorganised bone remodelling. Some patients are asymptomatic but others present with bone pain or other complications such as fracture and deformity. Major advances have been made in understanding the pathophysiology of PDB in recent years and highly effective agents are now available with which to suppress the abnormal bone turnover that causes the disease. In Chapter 1, an overview of the recent advances in the epidemiology, pathogenesis, clinical features and management of PDB is discussed. The clinical presentation of a cohort of patients with PDB and a systematic review and time trend analysis examining the way in which patients with PDB come to medical attention is discussed in Chapter 2. Chapter 3 provides a detailed analysis of randomised clinical trials examining and comparing the effects of various bisphosphonates used in the management of PDB. The long term effects of intensive treatment aimed at normalising ALP levels compared with a symptomatic approach using analgesia only initially is explored in Chapter 4. The change in ALP with bisphosphonate treatment and its relation to and impact on bone pain and quality of life scores as measured using the Short Form Survey 36-Item (SF36) questionnaire will be discussed in Chapter 5. In Chapter 6, I finally reflect upon the future challenges that remain to be overcome to explain the unusual distribution of the disease and to favourably alter the natural history and prevent the development of complications.

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Chapter 1

Introduction

Abstract

PDB is a common disorder characterised by increased but disorganised bone remodelling. Some patients are asymptomatic but others present with bone pain or other complications such as fracture and deformity. Major advances have been made in understanding the pathophysiology of Paget's disease in recent years and highly effective agents are now available with which to suppress the abnormal bone turnover that causes the disease. The recent advances in the epidemiology, pathogenesis, clinical features and management of Paget's disease will be reviewed and discussed in this chapter.

1.1 Introduction

PDB is a common metabolic disease characterized by increased and disorganised bone turnover affecting one or more skeletal sites. The classical description was by Sir James Paget in 1877 who described the clinical presentation and course of the disease in five patients naming the condition 'osteitis deformans'. [1] Sir James, an eminent surgeon and pathologist described 5 patients with a form of chronic bone disease and initially labelled these cases 'a chronic form of inflammation of the bones'. [1] One patient who he managed for over a period of 20 years presented initially with bone pain but gradually developed significant bone deformity involving his legs and skull. This patient eventually developed osteosarcoma within his forearm and died shortly after as a result of this. Sir James, on carrying out the post-mortem examination of this recently deceased patient identified bone samples on microscopy which appeared highly abnormal, demonstrating features consistent with accelerated bone turnover which he believed was due to an inflammatory process and which he termed 'osteitis deformans'. [1] Since Sir James' discovery from the 19th century, tremendous advances have been made in the understanding of the causes of PDB over recent years and treatments have been developed that are highly effective at suppressing the elevated bone turnover that is characteristic of the disease. However PDB continues to be associated with increased morbidity and mortality particularly from the complications that may develop as a consequence of this disease. Briesacher and colleagues previously undertook an analysis of healthcare costs between 2001-2002 incurred by patients with PDB in the United States using market research secondary care data sets of medical care claims, prescription drug claims and patient encounter (of health services) data; containing information on up to 6 million individuals. [2] Patients with PDB were identified by examining outpatient and inpatient claims records. A comparator group without a diagnosis of PDB was identified through an exact match procedure using gender,

age and comorbidity risk adjustment score (based on the presence of up to 189 medical conditions, except PDB in the diagnosis fields of claims records).[2] Each patient with PDB was matched to an individual without PDB but who had the same age, gender and the closest risk score. Expenditure records of 20 conditions/complications known to be associated with PDB were then calculated in patients with PDB and compared with patients in the comparator group without a diagnosis of PDB.[2] These included musculoskeletal complications, degenerative diseases, neurological and metabolic complications. Expenditure costs included costs of inpatient care, outpatient services and prescription drugs. In total 244 patients with PDB and 244 matched controls without PDB were identified. As expected, higher rates of complications were detected in patients with PDB including pathological fractures, low back pain, spinal stenosis and hearing loss. [2] The total spend by patients with PDB was $3.9 million compared to $3.3 million in matched controls. Out of these total figures, patients with PDB had significantly higher outpatient costs (Patients with PDB: $2.2 million, Matched Controls: $1.5 million, $p<0.05$) and prescription drugs costs (Patients with PDB: $220,831, Matched Controls: $79,082, $p<0.05$). [2] Inpatient costs were not significantly different between patients with PDB versus patients in the comparator group. [2] This study provides evidence in support of the higher healthcare costs accrued by patients with PDB for symptoms and complications associated with this disease as compared with patients without PDB.[2]

1.2 Epidemiology

There are marked ethnic and geographical variations in the occurrence of PDB. The highest prevalence is found in the UK, but the disease is also common in Spain, Italy, France, North America, Australia and New Zealand. [3-5] Within these countries there are also localized areas of higher prevalence such as the North West of

England [5] and Vitugudino in Spain. [6] The high frequency of PDB in Australia and New Zealand is thought to be attributable to the migration of white British nationals to these countries in the early 18th–20th centuries. Conversely, PDB is rare in the Indian subcontinent, Southeast and East Asia as well as in Scandinavia. [3-6]

In the UK, PDB affects between 1% and 2% of the population aged 55 and over but the prevalence increases with age to affect ~8% of the population by the eighth decade. [3-5] Van Staa and colleagues analysed the General Practice Research database in England and Wales and found that in addition to an increased incidence and prevalence with age, PDB was also associated with greater mortality compared to matched controls. [4] This is in contrast to the findings of Wermers and colleagues who studied 236 patients with PDB in Minnesota and identified a slightly improved overall survival ($p=0.010$) by 10 years after diagnosis in patients with PDB compared to white Minnesota residents of similar age and gender without PDB. [7] Analysis of patients with PDB in Salamanca and Vitigudino in Spain by Corral-Gudino and colleagues found an increase in the number of referrals of patients with PDB between 1986 and 2003 but a decline latterly between 2004 and 2009 in Vitigudino. [8] The authors noted that the referral pattern was similar at all times in Salamanca and that the severity of disease at presentation had reduced in both regions. [8]

A recent systematic review of the epidemiology of PDB concluded that the incidence and severity of new cases of PDB has declined in recent years in most countries with the exception of Italy. [6] The cause of this is unclear but changes in global migration patterns with an increased immigration from areas of low incidence such as South Asia to the UK and North America; a more sedentary lifestyle, improved nutrition and reduced exposure to infections have all been offered as possible explanations for this phenomenon. [6]

1.3 Pathogenesis

1.3.1 Normal bone structure

The human skeleton is formed of 2 types of osseous tissue namely cortical (compact) and cancellous (trabecular/spongy) bone. Cortical bone forms the outer cortex of bone and is hard, dense and strong. These qualities are essential in facilitating the various functions of the human skeleton. Cancellous bone is softer, weaker and less dense contributing to the flexible nature of the human skeleton. Cancellous bone is highly vascular and contains bone marrow.

Normal bone remodelling consists of a highly regulated and orderly cellular interaction between osteoblasts, osteoclasts and osteocytes. Osteoblasts originate from mesenchymal stem cells. Their primary function is to form new bone matrix via the secretion of collagen and proteins such as osteopontin and osteocalcin. Osteoblasts which become embedded in to the bone matrix newly formed are termed osteocytes. Osteocytes are the most frequently encountered cell in bone tissue. Together with osteoblasts, osteoclasts and osteocytes participate in the process of bone remodelling via the Receptor activator of nuclear factor kappa-B/ Receptor activator of nuclear factor kappa-B Ligand/Osteoprotogerin (RANK/RANK-L/OPG) signalling pathway described below. Osteoclasts often contain up to 5 nuclei and originate from macrophages; which in turn originate from the myeloid/monocyte lineage in the bone marrow. Their primary function is in the resorption of bone which involves dissolving bone crystalline hydroxyapatite and degrading the collagen-rich bone matrix.

1.3.2 Cellular and molecular changes in PDB

Bone turnover is markedly increased in bones that are affected by PDB. A histological analysis of bone samples of 754 patients with PDB from the Hamburg Bone Register was previously undertaken by Seitz and colleagues. [9]

Histomorphometric analysis of bone samples demonstrated the presence of increased trabecular number (but not trabecular thickness), an increase in osteoid volume and surface and increase in fibrotic tissue in bone samples of PDB patients above. [9] Analysis of cells within these bone samples revealed an almost 10-fold increase in osteoblast number and surface; all with normal morphology, and a significant increase in osteoclast number and surface with abnormal appearances including an increased size and large number of nuclei. [9]

Accumulating evidence suggests that the elevated bone turnover in PDB is caused by abnormalities in the molecular pathways that regulate osteoclast activity. Osteoclast differentiation and function is critically dependent on interactions between three molecules; RANK which is encoded by the Tumour Necrosis Factor Receptor Superfamily member 11a (*TNFRSF11A)* gene, RANKL, encoded by the *TNFSF11* gene and OPG, encoded by the Tumour Necrosis Factor Receptor Superfamily member 11b *(TNFRSF11B)* gene. In addition to these, a variety of other important molecules (described below) primarily expressed on osteoblasts also play an important role in osteoclast function and development. The RANK receptor is expressed by osteoclasts and osteoclast precursors; RANKL is produced by osteocytes, activated T-cells, osteoblasts and bone marrow stromal cells and OPG is produced by osteoblasts and other cell types. [10,11] Binding of RANKL to RANK promotes osteoclast differentiation and bone resorption whereas OPG inhibits these processes by acting as a decoy receptor for RANKL. [10,11] Outwith the RANK/RANK-L/OPG pathway, osteoclast differentiation is also dependant on stimulation by Macrophage-Colony Stimulating Factor (M-CSF), an important protein expressed by osteoblasts. The production of Wnt by osteoblasts has been found to promote the expression of RANK in osteoclast precursors. [12, 13] Wnt binds to 2 distinct receptor complexes resulting in the activation of 2 signalling pathways: a beta-catenin dependent (canonical) pathway and a beta-catenin independent (non-canonical) pathway. [12, 13] The canonical pathway arises from the interaction between Wnt and a complex of Frizzled and low density Lipoprotein

Receptor-related Protein (LRP) 5/6. [12, 13] Loss-of-function mutations in the LRP5 gene have been found to result in a reduction in osteoblast number, leading to loss in bone mass. [12, 13] The non-canonical pathway arises when Wnt5a binds to Receptor tyrosine kinase-like Orphan Receptor (ROR2) expressed on osteoclast precursors resulting in the increased expression of RANK on osteoclast precursors. [12, 13]
In PDB, the up-regulation of RANK expression results in osteoclast precursors which have increased sensitivity to RANKL resulting in enhanced osteoclast activation and bone resorption. The increased rates of bone formation in PDB are thought to be secondary to the increase in bone resorption but there is some evidence that cells of the osteoblast lineage may also be abnormal. [14] Although bone formation is increased in PDB, the newly formed bone is abnormal and has reduced mechanical strength, predisposing to the occurrence of fractures and deformity. [11]

1.3.3 Genetic factors in PDB

Linkage studies in families and genome-wide association and sequencing studies have identified several genes and loci that predispose to PDB and related syndromes. Potential candidate loci on chromosomes include 1p13, 5q35, 10p13,18q21, 8q24, 15q24, 14q32, 9p21, 8q22 and 7q33. Most of the implicated genes on the above loci are known to play a role in osteoclast differentiation and function (Figure 1.1)

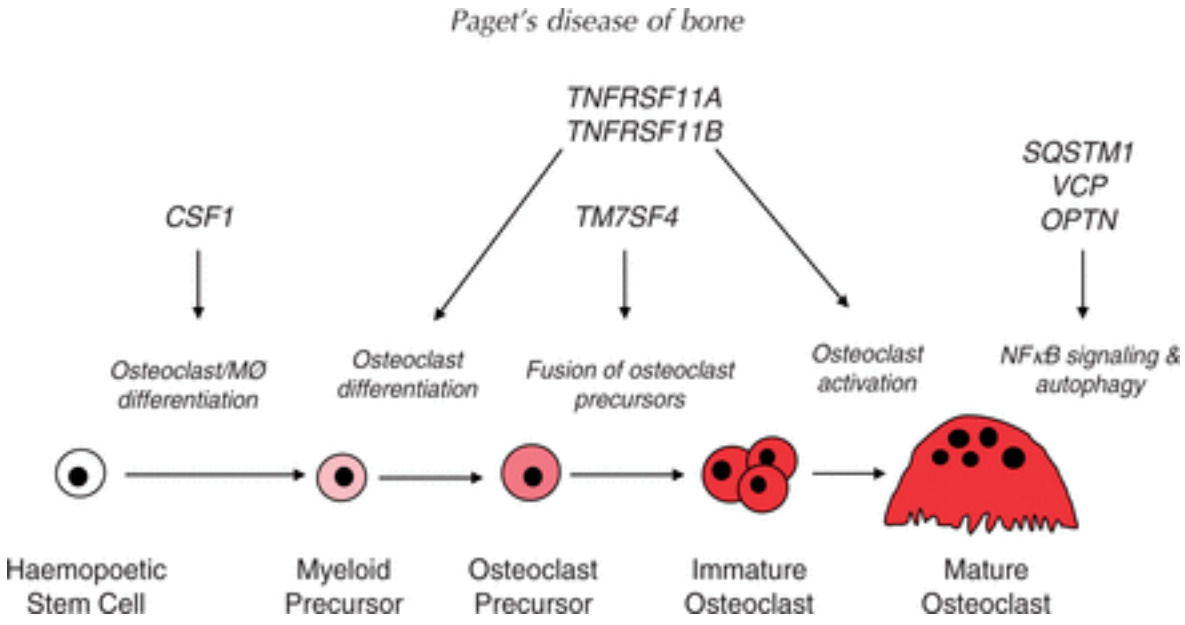


Figure 1.1: Genes that predispose to Paget's disease and related syndromes. Candidate genes for PDB and related syndromes are shown. The Colony Stimulating Factor *(CSF1)* gene, which encodes M-CSF, promotes differentiation of stem cells to cells of the osteoclast/macrophage lineage. The *TNFRSF11A* and *TNFRSF11B* genes encode RANK and OPG, respectively; both proteins play a key role in regulating osteoclast differentiation and activity. The Transmembrane 7 superfamily member 4 (Dendritic cell-specific transmembrane protein*) [TM7SF4 (DCSTAMP)]* gene is essential for fusion of osteoclast precursors to form mature osteoclasts. The Sequestosome 1 (*SQSTM1),* Valosin Containing Protein *(VCP)* and Optineurin *(OPTN)* gene products all play roles in regulating Nuclear factor kappa B (NFκB) signalling and autophagy in osteoclasts and are thought to play a role in osteoclast activation. (Adapted from Ralston and Layfield [11])

The most important susceptibility gene for classical PDB is *SQSTM1* located within the 5q35 locus. [15] A wide variety of mutations have now been identified and it has been estimated that up to 40% of patients with a family history of PDB and 10% of patients with 'sporadic' PDB carry a mutation in this gene. [11] The causal mutations cluster in the Ubiquitin (UBA) domain of the protein and inhibit its ability to bind ubiquitin. This in turn causes up-regulation of NFκB signalling and osteoclast activation by mechanisms that are still incompletely understood. [11] From a clinical perspective, patients with SQSTM1 gene mutations have more severe and extensive disease and a higher rate of complications than patients without SQSTM1 mutations. [15,17] It has also been noted that risk alleles have additive effects, resulting in a higher risk of developing PDB and more extensive disease in those that carry the highest number of risk alleles. [16,17]

Other candidate genes for classical PDB include CSF1 on chromosome 1p13, which encodes macrophage colony-stimulating factor (M-CSF), TNFRSF11A on chromosome 18q21, which encodes RANK, TNFRSF11B on chromosome 8q24, which encodes OPG, OPTN on Chromosome 10p13, which encodes optineurin, promyelocytic leukaemia (PML) on Chromosome 15q24, Rab and Ras Interactor 3 (RIN3) on chromosome 14q32; and VCP on Chromosome 9p21, which encodes valosin containing protein. The *TM7SF4 (*DCSTAMP) gene located on chromosome 8q22, and the 7q33 locus, have also been identified as potential candidates for PDB.[16]

1.3.4 Familial PDB-like Syndromes

The genetic basis of several rare syndromes with clinical features that mimic PDB have also been clarified. Activating mutations in *TNFRSF11A* cause the syndromes of Familial Expansile Osteolysis (FEO), early onset familial Paget's disease and Expansile Skeletal Hypophosphatasia (ESH); loss of function mutations in *TNFRSF11B* causes juvenile PDB [11] and loss of function mutations in VCP cause the syndrome of Inclusion body myopathy, Paget's disease and frontal-temporal

dementia (IBMPFD). [10] All of the familial PDB-like conditions (except juvenile PDB which is an autosomal recessive disorder) above are inherited in an autosomal dominant manner.[18, 19] FEO causes deafness in childhood, destruction of dentition in adulthood and bone pain, fracture and deformity. [18, 19] Families with FEO have been identified and reported in Northern Ireland, Germany, USA and Spain. Early onset familial PDB typically manifests with hearing impairment, tooth loss, bone pain and deformity with the axial skeleton more commonly affected as compared to FEO. [18, 19] One member of the Japanese family in which this condition was identified developed transient hypercalcaemia during periods of immobilization. [18, 19] ESH results in hearing and tooth loss during childhood or early adult life, bone pain, and osteolytic and sclerotic lesions affecting the appendicular skeleton and hands. [18, 19] Juvenile PDB, which involves missense and nonsense mutations in coding exons or gene deletions involving TNFRSF11B, results in hearing loss, fractures, bone deformity and hypercalcaemia. [18, 19] Premature death from cardiovascular disease in juvenile PDB has been reported. IBMPFD results in proximal myopathy and characteristic features of classical PDB; but with the addition of dementia in mid-life. [18, 19]

These observations indicate that genetic variations in the pathways that regulate osteoclast activity are most likely responsible for the abnormalities of osteoclast morphology and activity that are characteristic of PDB and related syndromes.

1.3.5 Environmental factors

Environmental factors are also important in PDB as reflected by the fact that incidence and severity of the disease have reduced in many countries over recent years. [11] The most widely studied potential environmental trigger for PDB is viral infection. The viral hypothesis stemmed from the observation that PDB osteoclasts frequently contain inclusion bodies that were thought to resemble the paramyxovirus nucleocapsid. However attempts to isolate viral nucleic acids from affected tissue have yielded contradictory results. [10, 11] Other suggested

predisposing environmental triggers include dietary calcium deficiency during childhood; [20] vitamin D deficiency and childhood rickets; [21] excessive mechanical loading of the skeleton [22] and environmental pollutants. [23]

1.4 Clinical Features

Bone pain is the commonest symptom of PDB. [7,24] It is classically described as unrelenting, more severe at night, not worsened by exercise and not alleviated with rest. However these features are not always present in clinical practice and it is often difficult to differentiate the pain of PDB from that of complications such as co-existing osteoarthritis. Therefore patients with PDB require thorough clinical assessment to determine the likely cause of the pain. This is important as treatments such as bisphosphonates only help pain that is due to increased metabolic activity.

Other presentations include deformity, fractures and neurologic complications such as headache, hearing loss, nerve compression syndromes and spinal stenosis [7,24] PDB is associated with a substantially increased risk of osteosarcoma but this complication is rare, occurring in less than 0.5% of patients. [7,24] Secondary osteoarthritis is also common. This is thought to be due to a combination of abnormal biomechanical loading of joints due to deformity and osteosclerosis affecting subchondral bone.

Altman reported that 242 of 290 patients referred for evaluation of PDB had pain in relation to the musculoskeletal system with back pain being the commonest complaint. [24] Tan and Ralston found that bone pain was the commonest presenting complaint affecting 65 out of 88 patients (73.8%) followed by deformity (18.1%), deafness (7.9%) and pathological fracture (5.7%) in a study examining the clinical presentation of the disease. [25] This study demonstrated that 20 out of 88 patients analysed (22.7%) were completely asymptomatic at presentation with PDB identified incidentally. [25] A systematic review of case series of patients with PDB

as part of this study also found bone pain to be the commonest presenting feature followed by deformity, deafness and fracture and that pain was a more common feature in recent studies as compared to fracture which was commoner in studies undertaken between 1958-1999. [25] Werner de Castro and colleagues analysed 134 patients with PDB retrospectively in Brazil and reported the occurrence of bone pain in 77.9% and deformities in 13.4% in this cohort. [26] Complications including deafness, fracture, hydrocephalus and the cauda equina syndrome were all reported but occurred infrequently. [26] Hamdy and colleagues analysed 56 patients with PDB identified from the metabolic bone clinic and found that bone pain was the most common presenting symptom (60.7%) with the majority of cases of pain being attributed directly to PDB. [27] Bone deformity, reduced mobility, deafness, lethargy, loss of vision, cognitive deficit, sensation of warmth in limbs, ill fitting dentures and fracture were also clinical manifestations identified in this study. [27]
Sometimes PDB may be picked up as an incidental finding in patients who are having blood tests or x-rays for another reason. A previous population-based survey in the UK suggested that around 7% of patients with radiological evidence of PDB come to medical attention. [4]

1.5 Investigations

The diagnosis of PDB is often suspected by the finding of a raised serum Alkaline Phosphatase (ALP) in patients who have otherwise normal liver function, or on the basis of the typical x-ray findings of osteosclerosis and osteolysis disrupting the normal trabecular pattern in affected bone, cortical thickening and bone expansion. [3,28] The most frequently affected bones are the pelvis (70% of cases), femur (55%), lumbar spine (53%), skull (42%) and tibia (32%). [10,28] Bone scintigraphy is a useful technique to evaluate the extent of disease; demonstrating increased radionuclide

uptake in the region of abnormal bone, and can be followed up by targeted x-rays of abnormal areas that are symptomatic.

Serum total ALP is most commonly used to assess metabolic activity. Bone-specific ALP can also be used but offers no clear advantage over total ALP except in patients with liver disease. [29] A systematic review examining the various bone turnover markers in PDB found that Procollagen Type 1 Amino-terminal propeptide (P1NP), total ALP, bone ALP and urinary N-terminal telopeptide (NTx) were the most useful markers of disease activity in untreated patients whereas monitoring of P1NP, total ALP and urinary NTx were most useful after treatment is administered. [30] Reid and colleagues reported that total ALP, bone ALP and P1NP were suitable markers of bone formation in monitoring the effects of bisphosphonate therapy whilst NTx was found to be the best marker of bone resorption in an analysis of patients with PDB receiving ibandronate as well as placebo-treated controls. [29]

1.6 Management

The management of PDB requires a multidisciplinary approach. Drugs that suppress bone turnover (antiresorptive treatments) can be helpful in treating pain that is due to increased metabolic activity, but most patients also require analgesics and some require surgery to treat complications of the disease such as fractures and osteoarthritis.

1.6.1 Antiresorptive treatments

Bisphosphonates are the treatment of first choice for metabolically active PDB. [10,31,32] Bisphosphonates are synthetic analogues of pyrophosphate that bind to hydroxyapatite in bone. The substitution of an oxygen molecule (P-O-P) with a carbon molecule (P-C-P) between two phosphate molecules makes bisphosphonates resistant to degradation, becoming clinically useful.

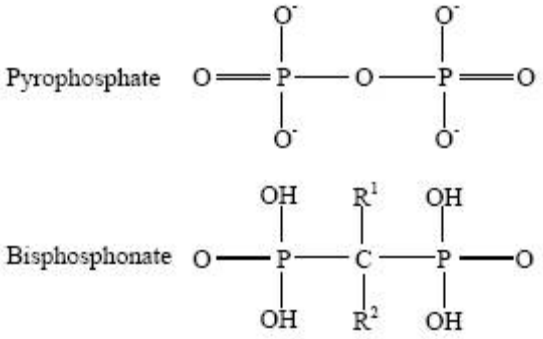


Figure 1.2: Chemical structure of pyrophosphate and bisphosphonate [33]

Clodronate, etidronate and tiludronate are examples of non-nitrogen containing bisphosphonates which function by becoming internalised by the osteoclast and becoming incorporated into toxic Adenosine Triphosphate (ATP) analogues, accumulating in the cytoplasm and causing cell death. [32] The newer nitrogen-containing bisphosphonates including alendronate, pamidronate, neridronate, risedronate, ibandronate and zoledronate inhibit the enzyme Farnesyl diphosphate (FPP) synthase causing the accumulation of Isopentenyl diphosphate (IPP) which become incorporated in to ATP analogues; and prevent prenylation of small Guanosine Triphosphate hydrolase enzyme (GTPase) proteins, both actions of which lead to osteoclast apoptosis. [32]

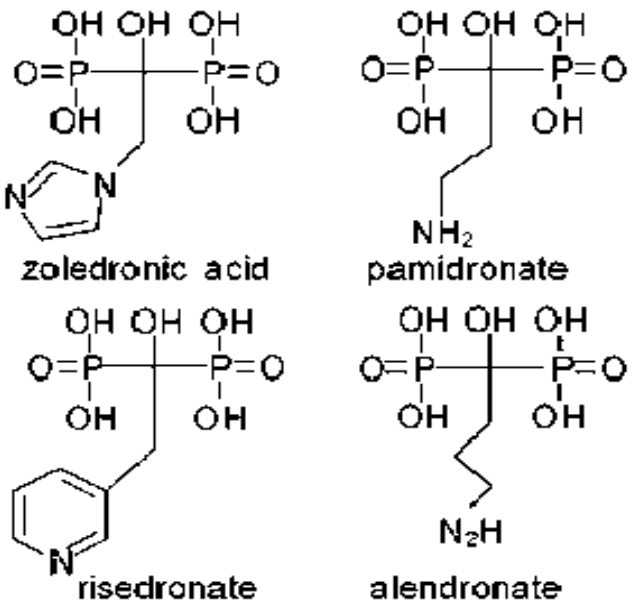


Figure 1.3: Chemical structures of amino-bisphosphonates [34]

Randomised trials comparing the effects of different bisphosphonates in the treatment of PDB have generally been short in duration and focused on the effects of treatment on biochemical markers of bone turnover. These studies have shown that the newer, more potent nitrogen-containing bisphosphonates are more effective than older bisphosphonates at suppressing bone turnover but few differences have emerged in symptomatic response between treatments.

Zoledronate has been shown to be superior to risedronate at suppressing biochemical markers of bone turnover in PDB and to improve some quality of life measures although the magnitude of effect was small. [35]

In another study intensive therapy with the bisphosphonate risedronate had no greater effect on quality of life, bone pain, deafness, fracture rates or the requirement for orthopaedic surgery as compared with symptomatic therapy despite the fact that ALP levels were much lower in the risedronate group. [36] This indicates that levels of bone turnover do not correlate well with symptom response or complications in PDB. Nowadays, most clinicians favour the use of aminobisphosphonates over older

bisphosphonates such as etidronate and tiludronate because of their greater efficacy at suppressing bone turnover. The most popular treatments are oral risedronate (30 mg daily for 2 months); intravenous pamidronate (60 mg on one to three occasions) and intravenous zoledronate (5 mg).

Intravenous bisphosphonates are associated with a transient flu-like illness and also carry a risk of inducing hypocalcaemia in patients with high bone turnover and pre-existing vitamin D deficiency. Because of this patients should be checked for vitamin D deficiency and given supplements if necessary.

Bisphosphonates are contra-indicated in patients with significant renal impairment. In these circumstances subcutaneous calcitonin (100 u s/c three times weekly) can be tried. [3] There are anecdotal reports of successful treatment of PDB with the RANKL inhibitor denosumab [37] but the drug is unlicensed for this indication.

1.6.2 Other medical treatments

Additional medications may be required to control pain. A variety of treatments are used in clinical practice including simple analgesics, opiates, gabapentin and amitriptyline.

1.6.3 Non-pharmacological treatments

Patients with bone deformity and limb shortening can benefit from shoe raises and walking aids. Surgical treatment may also be necessary to treat complications. Bisphosphonate therapy is usually administered prior to surgery in order to reduce the risk of bleeding during surgery. Results are generally good, but the procedures can be technically challenging due to bone deformity, osteosclerosis and increased vascularity. [38] A recent systematic review on spinal surgery of 17 patients with PDB involving the spine with associated nerve compression syndromes revealed that excessive bleeding was a frequent complication in patients who had not received bisphosphonate therapy pre-operatively and that the use of bisphosphonate therapy postoperatively resulted in improved outcomes in terms of recovery of

neurological function in patients who achieved only marginal benefit from surgery. [39]

1.7 Clinical guidelines

Current clinical guidelines recommend that the main indication for bisphosphonate therapy is treatment of bone pain thought to be due to increased metabolic activity of PDB. [3] Although recent Endocrine Society practice guidelines on PDB have recommended that patients with active PDB who are at risk of complications should be treated with a bisphosphonate there is no evidence as yet that bisphosphonates can prevent complications or alter the natural history of PDB. [40] These practice guidelines have also suggested that bisphosphonate treatment should be given with the aim of reducing the chosen biochemical marker to below the midpoint of the reference range in order to improve patient outcomes, although the authors of these guidelines acknowledge the lack of objective evidence in support of this suggestion. [40]

Chapter 2

Clinical Presentation of PDB: Evaluation of a Contemporary Cohort and Systematic Review

Abstract

This Chapter evaluates the presenting features of PDB in a contemporary cohort of UK patients. A systematic review of studies in which the presenting features has been reported was conducted. In the present case series, 88 patients with PDB referred to a specialist metabolic bone diseases clinic from 2005-2013 were identified. Bone pain was the most common presenting feature occurring in 73.8% of patients. Other features included bone deformity (18.1%), deafness (7.9%) and pathological fracture (5.7%). The disease was asymptomatic in 22% of cases. Antiresorptive treatment was given for pain in 34 cases and 61.7% of patients responded. Patients with a shorter disease duration were more likely to respond ($p = 0.047$). In the systematic review, bone pain was the most common presenting feature followed by deformity, deafness and fracture. Time trend analysis in subjects of European descent showed that fracture was less common in studies performed during the past 25 years as compared with older studies (5.5 vs 10.8% $p<0.001$) whereas pain was more common (54.3 vs 48.3%, $p = 0.003$). This study shows that while changes in the mode of presentation of PDB have occurred over recent years, many patients continue to present with complications such as fracture and deformity.

2.1 Introduction

PDB is a common metabolic bone disorder characterised by increased and disorganised bone remodelling affecting one or more skeletal sites. [41] Epidemiologic surveys have suggested that only 7 % of patients with radiological evidence of PDB come to medical attention suggesting that many affected individuals may be asymptomatic. [4] Patients that do present clinically have a highly variable mode of presentation however; in some cases, the disease is picked up as an incidental finding on blood tests or radiographs, whereas others present with specific complications such as bone pain, bone deformity, pathological fracture and deafness. [41] The mode of presentation has been reported in several case series, but these data have not so far been the subject of a systematic review. The incidence and severity of PDB have decreased in many [4, 42, 43] but not all [8,44] regions over the past 35 years. [6] It is currently unclear to what extent, if any, these secular changes have impacted on presentation of the disease. In order to gain an insight into this, the mode of presentation of PDB in a contemporary cohort of patients presenting with Paget's disease to a specialist UK clinic over an eight-year period between 2005 and 2013 was evaluated and a systematic review of studies in which the presenting clinical features of PDB were documented was conducted. This study was undertaken by the author (AT) and Prof. Stuart H Ralston (SHR). Author contributions are as follows:

Study conception and design: SHR
Acquisition of data: AT, SHR
Statistical analysis: SHR
Analysis and interpretation of data: SHR
Drafting of final manuscript: AT, SHR

2.2 Patients and Methods

The cohort study was conducted in consecutive patients referred to a specialist clinic for metabolic bone disease at the Rheumatic Diseases Unit, Western General Hospital, Edinburgh, UK, over an eight-year period between July 2005 and July 2013. The clinic serves a population of 780,000. Data were routinely collected on age at first diagnosis, family history of PDB, sites of involvement, musculoskeletal pain and its characteristics, fractures, osteosarcoma, use of a hearing aid, and previous treatment for PDB. Evidence of bone deformity was routinely assessed, and if present was recorded as being mild, moderate or severe. Blood samples were collected for routine biochemical analyses and for genetic studies.

The sites of involvement were defined by analysis of radionuclide bone scans and/or by skeletal radiographs. In all cases, the diagnosis of PDB was made on the basis of typical radiological features on radiographs of an affected site. [3] Mutation screening of the *SQSTM1* gene was carried out by Deoxyribonucleic Acid (DNA) sequencing of exons 7 and 8 and the intron–exon boundaries as previously described. [15]

The systematic review was conducted by searching Medline using the MESH major terms "Paget's disease of bone" or "osteitis deformans" and the keyword "clinical". 491 citations were retrieved and the titles and abstracts of these citations were reviewed. Only case series with >10 patients with a focus primarily on the clinical presentation of PDB were analysed and relevant data extracted focusing on complications such as presence of bone deformity, bone pain, deafness, and pathological fractures due to Paget's disease. The frequency with which fracture was a presenting feature of PDB in different countries was compared using country-specific rates of hip fracture in men and women that had previously been reported in the literature. [45-49]

2.2.1 Statistical Analysis

Between-group comparisons for ALP levels before and after treatment in the contemporary cohort study were assessed by the Wilcoxon test since the ALP data were not normally distributed as assessed by the Kolmogorov Smirnov test. [50, 51] Predictors of the response of pain to antiresorptive treatment in the contemporary cohort were assessed by binary logistic regression which makes no assumptions about the distribution of dependent variables. Differences in the proportion of patients with complications of PDB presenting in different regions and between different time frames across groups were assessed by the Chi-square test. The relation between frequency of Pagetic fractures as a presenting feature of the disease and country-specific hip fracture rates was assessed by Pearson's correlation. Statistical analysis was performed using Minitab version 12.0. It is acknowledged that due to the inherent risk of false positive results where multiple testing has been performed, a p value of <0.05 carries nominal significance.

2.3 Results

2.3.2 Clinical Characteristics of Study Population

A total of 88 patients were included in this study. Relevant clinical and demographic details of the patients at presentation are shown in Table 2.1. The majority were male and 10 (11.3 %) reported a family history of PDB. Fourteen patients (15.9 %) tested positive for *SQSTM1* mutations; in 13 cases the mutation was P392L and in one case G425R. Seven of the patients with *SQSTM1* mutations (50 %) had a positive family history of the disease. The median [interquartile range] ALP level at presentation was 193 IU/L [119–277] with a range of 45–2753 IU/L and 78.4 % of patients had an elevated level of ALP. The sites of involvement as assessed by bone scan and/or X-ray included the pelvis ($n = 62$; 70.4 % of cases); lumbar spine ($n = 22$; 25.0 %), femur ($n = 15$; 17.0 %), thoracic spine ($n = 10$; 11.3 %), skull ($n = 10$; 11.3 %), tibia ($n = 9$;

10.2 %), sacrum (*n* = 8; 9.1 %), humerus (*n* = 4; 4.5 %) and scapula (*n* = 3; 3.4 %). The most common presentation was with bone pain and in 37.5 % of cases this was thought to be caused by PDB. Five patients (5.7 %) with previously undiagnosed PDB presented with pathological fractures; sixteen (18.1 %) presented with bone deformity; and 7 (7.9 %) presented with deafness associated with skull involvement. In 20 patients (22.7 %) the disease had been picked up as an incidental finding.

Table 2.1: Clinical and demographic details of study population at presentation

Age	72.9+11.9
Age at first diagnosis	70.3+12.6
Male Gender	53 (60.2%)
Family history of PDB	10 (11.3%)
SQSTM1 mutation	14 (15.9%)
Caucasian	86 (97.7%)
Monostotic	46 (52.2%)
Bone pain	65 (73.8%)
Thought to be caused by PDB	33 (37.5%)
Not thought to be caused by PDB	22 (25.0%)
Origin uncertain	10 (11.3%)
Bone deformity	16 (18.1%)
Mild	6 (6.8%)
Moderate	6 (6.8%)
Severe	4 (4.5%)
Fracture of affected bone	5 (5.7%)
Deafness and skull involvement	7 (7.9%)
Osteoarthritis [1]	22 (25.0%)
Osteosarcoma	1 (1.1%)
No signs or symptoms	20 (22.7%)
ALP (Normal Range: 40-125 IU/L)	193 [119-277]

Values for age and age at diagnosis are mean +SD, values for ALP are median [interquartile range]. Other values are numbers and percentages

[1] Affecting a joint adjacent to an involved site

2.3.3 Response to Treatment

In total, 34 patients were commenced on antiresorptive treatment for bone pain. Of these subjects, 33 were given a bisphosphonate; 23 were treated with zoledronate, 8 with risedronate and 2 with pamidronate. One patient was given denosumab, which was prescribed off-label due to impaired renal function. Bone pain improved in 21 patients (61.7 %) following treatment. The median [interquartile range] ALP level before antiresorptive treatment was 193 [119–237] IU/L (range: 45–4974) and the median [interquartile range] ALP level after treatment was 70.5 [52.7–87] IU/L (range: 26–1122), a difference that was significant ($p < 0.001$). In order to identify predictors of improvement in bone pain, a binary logistic regression analysis was performed, entering baseline ALP, duration of PDB, gender and drug used into the model. This showed that the only significant predictor of a positive response of pain was duration of Paget's disease. Specifically patients with a shorter duration of PDB were more likely to respond in terms of bone pain (odds ratio 0.86, 95 % confidence interval 0.75–1.00, $p = 0.047$). Serum ALP level prior to treatment had no predictive value. Reflecting this observation, the median [interquartile range] pre-treatment ALP levels in subjects who had a positive pain response was 188 [93–414] and did not differ significantly from those who did not have a positive pain response 199 [127–263], ($p = 0.57$).

2.3.4 Systematic Review

The study selection process for the systematic review undertaken is illustrated in Figure 2.1. 491 potentially eligible papers were identified from the literature search but many were excluded for the reasons set out in Figure 2.1. During review of the full text papers, a further three relevant publications were identified that were not picked up by the literature search. In total, 24 eligible studies [7, 24, 26, 27, 44, 52-68] were identified. Relevant details of these are summarised in Table 2.2 along with data from the present study. One study, based in New Zealand [54], reported clinical features of PDB patients who originated from India and for the purpose of analysis,

this study was included with the studies from India. Table 2.3 summarises details of the mode of presentation, broken down by geographical region. Bone pain was the most common presenting symptom in all studies. In most regions, the prevalence of bone pain as a presenting symptom ranged between 40 and 55 % but in studies from South America and India the frequency of pain was greater than 70 %. The frequency of fracture as a presenting feature varied widely between different regions. It was lowest in South America with a frequency of 2.9 % and highest in India with a frequency of 27 %. For bone deformity the frequency in the UK was 16.2 % and values were similar in South America and the Far East. However in European studies, studies from the USA and studies from India, deformity was more common, ranging between 24.3 and 33.7 %. The frequency of deafness ranged from 5.5 to 11.2 %. In view of the marked differences between countries in the frequency with which fracture was reported as a presenting feature of PDB, a further analysis was performed in which fracture frequency in PDB was correlated with previously reported hip fracture rates in different countries [14,45-48]. The results are summarised in Table 2.4 and Figure 2.2. When all data were considered no correlation was found between the rates of Pagetic fracture and rates of hip fracture from the same country in women ($r = 0.03$, $p = 0.92$) or men ($r = 0.47$, $p = 0.17$) (Table 2.4). However, when data from the Indian studies were excluded, where the Pagetic fracture rates were more than double those observed in other countries, there was a significant correlation with country-specific hip fracture rates in women ($r = 0.82$, $p = 0.007$) and in men ($r = 0.67$, $p = 0.048$) (Figure 2.2).

Since the frequency of PDB has fallen in many countries over recent years [42, 43], the mode of presentation in studies performed before 2000, between 2000 and 2009 and after 2010 was evaluated. This analysis was restricted to studies where the patients were of European descent in view of the differences that were observed between clinical features in studies from India and the Far East. The results are shown in Table 2.5. Bone pain was more common as a presenting feature in studies performed between 2010 and 2014 (65.3 %) as compared with between 2000 and 2009

(50.4 %) and before 2000 (48.3 %) ($p < 0.01$). Conversely, fracture was less common with the prevalence falling from 10.8 % in 1958–1999 to 6.5 % between 2000 and 2009 and 3.8 % after 2010 ($p < 0.01$). There was no clear pattern with regard to bone deformity; the frequency was 21.8 % in the studies performed between 1958 and 1999 as compared with 26.5 % in the studies conducted between 2000 and 2009 and 10.1 % in the studies conducted since 2010. The prevalence of deafness was similar in the most recent timeframes (11.1 and 6.7 %). Comparison with older studies was limited by the fact that the frequency of deafness had only been recorded in one study of patients of European descent performed before 2000.

Figure 2.1: Flow diagram of the systematic review process

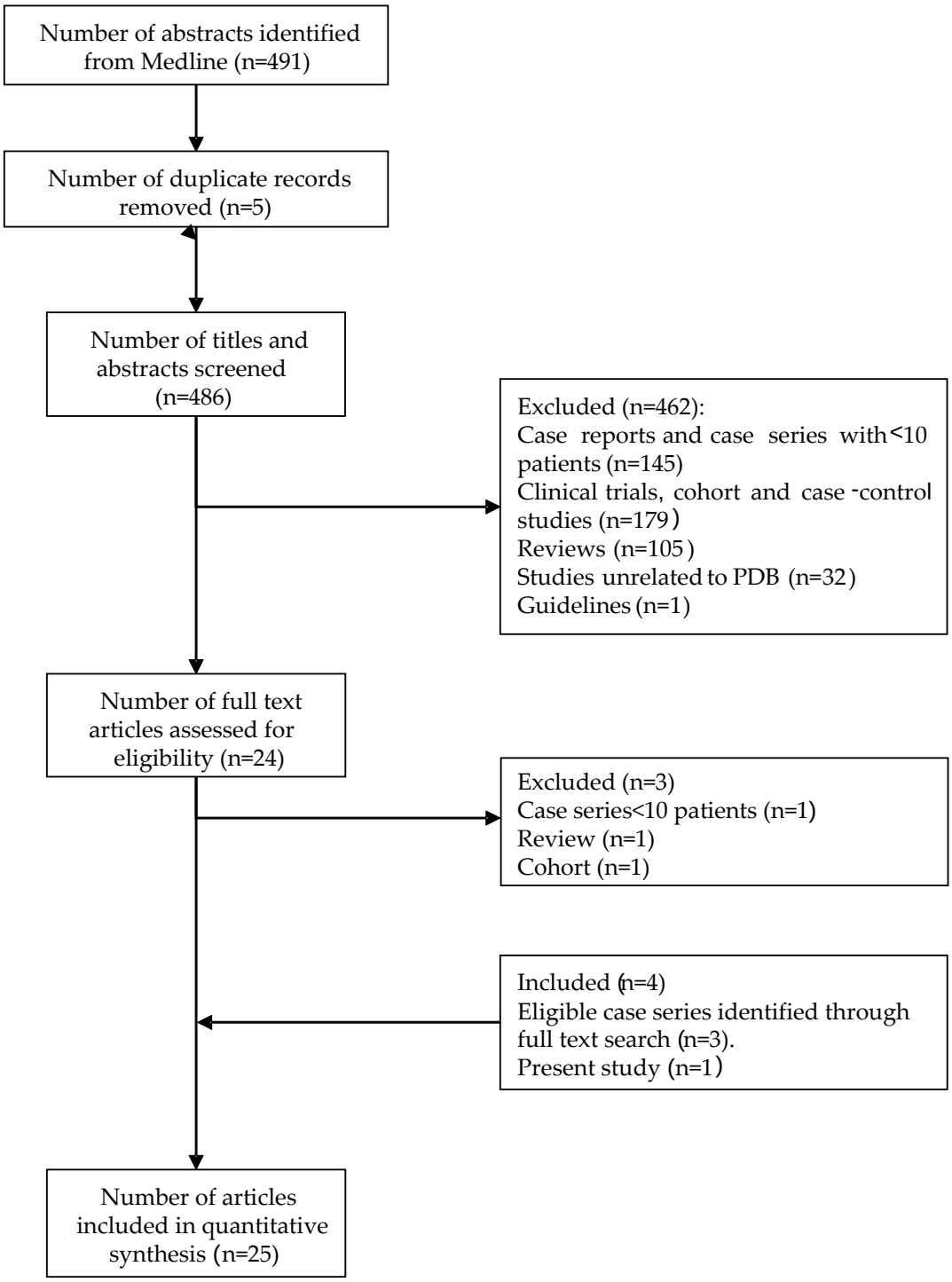


Table 2.2: Details of studies included in Systematic Review

Author	Location	Year	N=	Bone Pain	Monostotic	Deformity	Fracture	Deafness
Tan (present study)	UK	2014	88	65 (73.8%)	46 (52.2%)	16 (18.1%)	5 (5.7%)	7 (7.9%)
Werner de Castro [26]	Brazil	2012	134	104 (77%)	34 (25%)	18 (13.4%)	4 (3%)	11 (8.2%)
Gu [53]	China	2012	13	12 (92.3%)	5 (38.4%)	1 (7.7%)	0 (0%)	2 (15.3%)
Sankaran [54]	New Zealand*	2011	14	8 (57.1%)	6 (42.8%)	N/A	N/A	N/A
Varenna [55]	Italy	2010	224	124 (55%)	97 (43%)	3 (1.3%)	9 (4%)	N/A
Bandeira [56]	Brazil	2010	108	69 (63.9%)	42 (38.8%)	19 (17.6%)	3 (2.8%)	4 (3.7%)
Del Pino-Montes [52]	Spain	2009	602	391 (64.9%)	N/A	114 (18.9%)	29 (4.8%)	68 (11.3%)
Wermers [7]	USA	2008	236	95 (40.2%)	65 (27.5%)	31 (13.1%)	6 (2.5%)	52 (22.0%)
Hashimoto [57]	Japan	2006	169	88 (52%)	87 (51.4%)	24 (14.2%)	16 (9.4%)	8(4.7%)
Anjali [58]	India	2006	51	30(65.2%)	5 (9.8%)	15 (32.6%)	9 (19.6%)	3 (6.5%)
Bhadada [59]	India	2006	21	19 (90.5%)	6 (28.6%)	4 (19%)	6 (28.6%)	4 (19%)
Joshi [60]	India	2006	17	15 (88.2%)	1 (5.8%)	11 (65%)	9 (53%)	0 (0%)
Rendina [44]	Italy	2006	236	126 (53%)	85 (36%)	162 (68.6%)	20 (8.4%)	0 (0%)

Holgado [61]	Spain	2005	18	N/A	5 (28%)	5 (27%)	N/A	N/A
Merlotti [62]	Italy	2005	147	27 (18.4%)	62 (42%)	15 (10.2%)	15 (10.2%)	9 (6.1%)
González [63]	Chile	2003	15	13 (86.6%)	8 (53.3%)	5 (33.3%)	N/A	N/A
Guma [64]	Spain	2002	314	135 (43%)	113 (36%)	N/A	N/A	42 (13.3%)
Wang [65]	Ireland	2002	24	7 (29%)	8 (33.3%)	N/A	3 (12.5%)	N/A
Davie[66]	UK	1999	889	N/A	N/A	174 (19%)	107 (12%)	N/A
Monfort [67]	Spain	1999	189	143 (75.6%)	38 (20.1%)	N/A	N/A	N/A
Hamdy [27]	USA	1993	56	34 (60.7%)	N/A	15 (26.7%)	3 (5.3%)	7 (12.5%)
Winfield [68]	UK	1984	50	24 (48%)	N/A	1 (2%)	3 (6%)	N/A
Altman [24]	USA	1980	290	135 (46.5%)	N/A	130 (45%)	46 (15.8%)	7 (2.4%)
Galbraith [69]	UK	1977	285	84 (29.5%)	N/A	22 (7.7%)	17 (5.9%)	N/A
Klimova [70]	Russia	1958	238	N/A	100 (42%)	N/A	19 (8%)	N/A

N/A: Data not available * Patients were of Indian descent

Table 2.3: Mode of presentation of PDB by Region

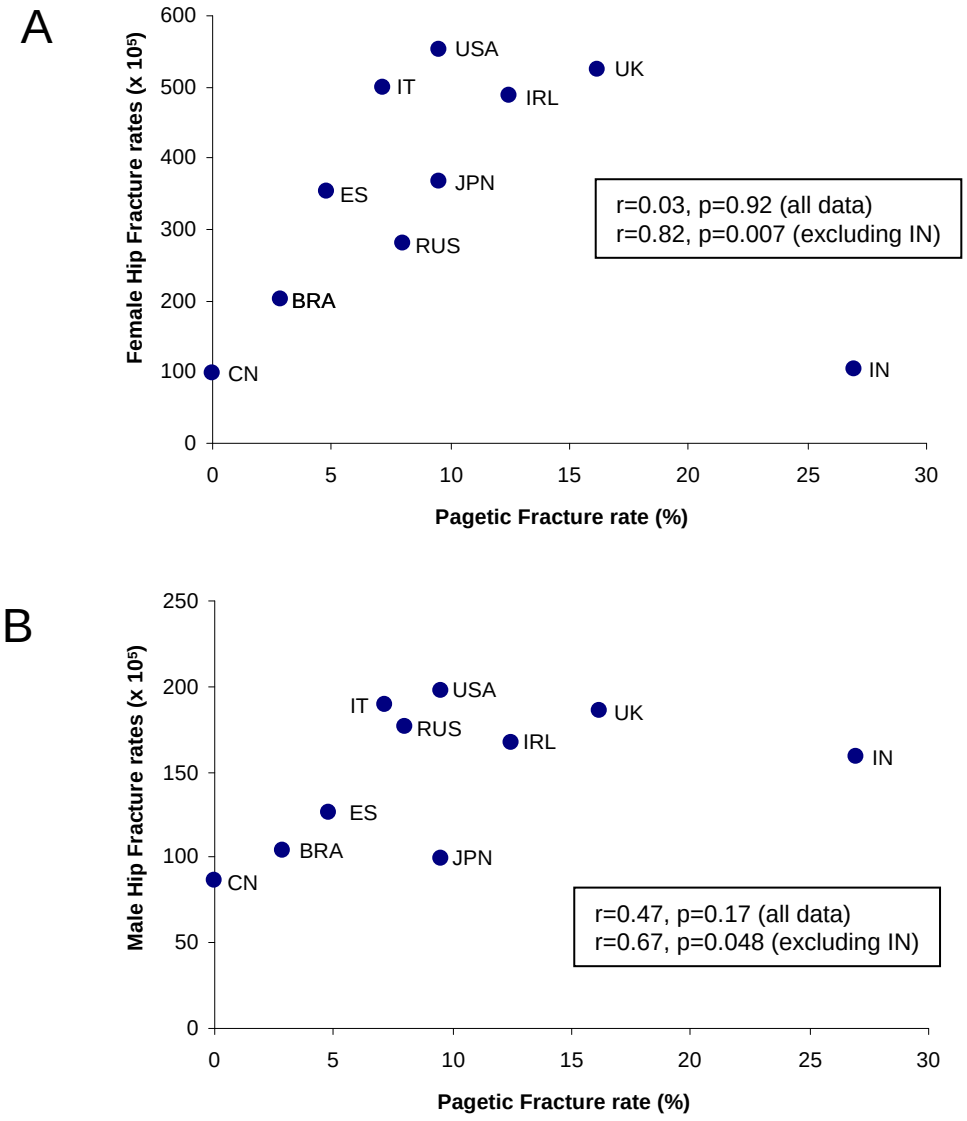
	Number of Studies	**Number of Patients**	**Bone Pain**	**Fracture**	**Deformity**	**Deafness**
UK	5	1336	180/447 (40.3%)	135/1336 (10.1%)	213/1312 (16.2%)	7/88 (8.0%)
Europe	8	1968	803/1523 (52.7%)	92/1447 (6.4%)	299/1227 (24.4%)**	119/1063 (9.2%)
South America	3	257	186/257 (72.4%)**	7/242 (2.9%)**	42/257 (16.3%)	15/242 (6.2%)
India	4	103	77/103 (74.8%)**	24/89 (31.2%)**	30/89 (33.7%)**	7/89 (7.9%)
Far East	2	182	100/182 (54.9%)**	16/182 (8.8%)	24/182 (13.2%)	10/182 (5.5%)
USA	3	582	264/582 (45.4%)	55/582 (9.5%)	176/582 (30.2%)**	59/526 (11.2%)
All studies	*23*	*4215*	*1603/3070 (38.0%)*	*326/3854 (10.6%)*	*784/3649(20.3%)*	*217/2426 (5.9%)*

The values in the table refer to the number of individuals who had the complication in relation to the total number of individuals where information was collected on the complication of interest. The frequencies of complications were significantly different between regions ($p < 0.0001$ for bone pain, fracture, and deformity and $p = 0.043$ for deafness) Significant differences for pairwise comparisons between regions for individual complications as compared with values in the UK are indicated by * $p < 0.05$, ** $p < 0.01$

Table 2.4: Relation between Pagetic fractures and country specific hip fracture rates

			Hip fracture rates, per 100,000 population		
Country	Studies included	Pagetic Fracture (%)	Female	Male	Source of hip fracture data
Brazil	[26, 56]	2.9	202	104	Morales-Torres 2004 [14]
China	[53]	0.0	97	87	Dhanwal 2010 [46]
India	[58-60]	27.0	105	159	Dhanwal 2013 [45]
Ireland	[65]	12.5	488	167	Svedbom 2013 [47]
Italy	[44, 55, 62]	7.2	189.5	498.5	Svedbom 2013 [47]
Japan	[57]	9.5	368	99.6	Dhanwal 2010 [46]
Russia	[70]	8.0	279	176	Lesnyak 2012 [48]
Spain	[52]	4.8	353	125.9	Svedbom 2013 [47]
UK	[25, 66, 68, 69]	16.2	523	186	Svedbom 2013 [47]

Figure 2.2: Correlation between Pagetic fracture and country-specific hip fracture rates in men and women.



Panel A: Relation between reported proportions of patients who presented with a Pagetic fracture in relation to country specific rates of hip fracture in women. **Panel B:** Relation between reported proportions of patients who presented with a Pagetic fracture in relation to country specific rates of hip fracture in men. Data from different countries are indicated as follows: CN- China; BRA –Brazil; ES – Spain; IT- Italy; RUS- Russia; JPN – Japan; USA – United States of America; IRL – Ireland; UK – United Kingdom; IN – India. Spearman correlation co-efficients are shown for all data and the data excluding India.

Table 2.5: Mode of presentation of PDB by time frame

	Number of Studies	Number of Patients	Bone Pain	Fracture	Deformity	Deafness
1958-1999	7	1997	420/870 (48.3%)	195/1808 (10.8%)	342/1570 (21.8%)	7/290 (2.4%)
2000-2009	8	1592	787/1574 (50.4%)	64/985 (6.5%)**	332/1254 (26.5%)**	171/1535 (11.1%)**
2010-2014	4	554	362/554 (65.3%)**	21/554 (3.8%)**	56/554 (10.1%)**	22/330 (6.7%)*

The values in the table refer to the number of individuals who had the complication in relation to the total number of individuals where information was collected on the complication of interest. The table includes data from European studies only (see text for details). The frequency of complications was significantly different between timeframes for all variables ($p < 0.0001$). Significant differences for pairwise comparisons between timeframes for individual complications as compared with the 1958–1999 timeframe are indicated by * $p < 0.05$, ** $p < 0.01$

2.4 Discussion

In this study, the mode of presentation of PDB in a case series of 88 patients who had presented to a regional referral centre over an 8-year timeframe was reviewed and a systematic review was conducted on previous studies where the mode of presentation of PDB had been documented.

Most patients in the present study were symptomatic or had complications. Bone pain was the commonest symptom, occurring in about 74 % of cases although in one-quarter of these patients the pain was considered to be due to co-existing osteoarthritis. Co-existing osteoarthritis is a common cause of pain in PDB, although other potential causes include nerve compression syndromes, fibromyalgia, and chronic pain syndrome. Many patients in the present series also had complications of the disease at presentation; 18.1 % had bone deformity; 5.7 % had a pathological fracture and 7.9 % had deafness. This illustrates that a substantial proportion of PDB patients have irreversible skeletal damage by the time the diagnosis is made.

In this study, 61.7 % of patients who were considered clinically to have pain related to PDB responded to antiresorptive therapy. Logistic regression analysis showed that the only significant predictor of a response of pain was duration of the disease. This suggests that with increasing disease duration, there is a diminished likelihood of bone pain being due to increased metabolic activity of PDB and a greater likelihood of it being due to complicating conditions such as osteoarthritis. [41] These observations are in keeping with those of previous investigators who have also noted that there may be dissociation between bone pain in PDB and metabolic activity as assessed by ALP levels. [36, 71, 72]

In the systematic review, bone pain was also the most common presenting feature but differences were observed between regions and with time. Notably bone pain was a more common presenting feature in the series from India and South America as compared with other regions and was significantly more common in studies

performed between 2010 and 2014 as compared with previous decades. Differences were also noted in the prevalence of fracture as a presenting feature; fractures were less common in South American studies but much more common in studies from India where the rate was more than double that observed in most other countries. When the rates of fracture as a presenting feature of PDB were correlated to the reported rates of hip fracture in the same countries, a significant correlation between Pagetic fractures and hip fractures was observed, but only when the studies from India were excluded. This is of interest since it suggests that in many countries, there may be shared factors which contribute to the variation in osteoporotic fractures and Pagetic fractures, although further work will be required to investigate what those factors might be.

A further feature of interest was the observation that the prevalence of fracture as a presenting feature of PDB has fallen over recent decades. This may have been partly attributable to the observation that two of the four studies performed between 2010 and 2014 were from South America where the fracture rates were lower than in other regions. The frequency of bone deformity in the systematic review was highly variable and there was no consistent pattern of changes with time. Similarly there was no consistent pattern with region or time with regard to the frequency of deafness, although interpretation was limited due to the lack of information on deafness in the earlier studies.

The results of the systematic review need to be treated with caution because of differences in referral patterns between regions, missing data and reporting bias. The results are of some interest however in demonstrating that the clinical presentation of PDB may have changed over recent years with an increasing frequency of bone pain and decreasing frequency of pathological fractures.

While PDB is often considered to be a benign disease, the present study indicates that a sizeable proportion of patients present with complications. These results confirm findings reported in the Paget's disease Randomised trial of Intensive versus Symptomatic Management (PRISM) study in which PDB patients recruited

from secondary care across the UK experience significant morbidity and reduced quality of life. [36, 73] Since there is no evidence that bisphosphonates can reverse complications of PDB once these are established [36, 41] this highlights the need to develop better methods of detecting PDB at an earlier stage, before skeletal damage has occurred. In this regard, disease severity and extent can be predicted by genotyping for *SQSTM1* mutations and other risk alleles [15, 74] and this would be a potential avenue for future research. Although the effects of bisphosphonate therapy on the natural history of PDB are unclear, a study is in progress (the ZIPP trial ISRCTN 11616770) to determine if genetic testing can be combined with prophylactic bisphosphonate therapy to prevent or delay the onset of disease. If this was found to be beneficial then a wider programme of testing coupled to targeted intervention might be helpful in reducing skeletal morbidity associated with this common disease.

Chapter 3

The effects of Bisphosphonate therapy on clinical outcomes in PDB: A Meta-Analysis

Abstract

Bisphosphonate therapy in patients with PDB has been shown to effectively reduce circulating serum ALP levels. Many experts believe that suppression of metabolic bone activity should translate in to improved clinical outcomes although there has not been any strong supporting evidence in favour of this opinion. This chapter describes a meta-analysis which was undertaken to gather all available published evidence in order to determine whether the use of bisphosphonate therapy really does improve clinical outcomes and/or prevent the development of relevant complications; and also to assess how harmful bisphosphonate therapy is in patients with PDB.

3.1 Introduction

The medical treatment of PDB is based on drugs that inhibit the increased osteoclastic bone resorption that characterises this disease. Bisphosphonates are considered to be the treatment of choice for PDB because they are highly effective at suppressing this elevated bone turnover. The principal indication for antiresorptive therapy is localised bone pain thought to be caused by increased metabolic activity. [3] Aminobisphosphonates have greater inhibitory effects on bone turnover in PDB than simple bisphosphonates and offer the prospect of reducing bone turnover to normal levels in a greater proportion of patients than is possible with simple bisphosphonates. [75, 76] In addition, bone biopsy studies have shown that aminobisphosphonate therapy can restore the architecture of newly formed bone to normal. [77] This raises the possibility that the more potent bisphosphonates, by providing greater inhibition of bone turnover, may be able to prevent long term complications of the disease such as the progression of deafness, bone deformity, fractures and progression of osteoarthritis. Many experts believe that bisphosphonate therapy should be administered with the aim of normalising bone turnover in the hope that this will arrest disease progression and prevent the development of complications such as facial deformity, deafness when the skull base is affected, and spinal cord dysfunction in patients with spinal PDB. [3] However, there are insufficient data to determine whether maintaining alkaline phosphatase levels within the normal range reduces the risk of complications. There is also no evidence that asymptomatic patients benefit from antiresorptive therapy. [36]

The aim of this systematic review and meta-analysis commissioned by the Cochrane Collaboration [involving the author (AT) and 2 other colleagues-Dr. Luis Corral-Gudino (LCG) and Prof. Stuart H Ralston (SHR)] was to gather all published evidence available in order to determine if bisphosphonate therapy improves clinical outcomes or prevents complications, in addition to its previously widely

demonstrated effect on suppression of biochemical markers of bone turnover. The following are the contributions made by each author:

Drafting the protocol: LCG, SHR
Study Selection: AT, LCG
Extracting data from studies: AT, LCG
Entering data into Review Manager 2014: LCG
Carrying out the analysis: LCG
Interpreting the analysis: LCG, SHR
Drafting the final review: AT, LCG, SHR
Disagreement resolution: SHR
Updating the review: AT, LCG

3.2 Objectives

The primary aim of this systematic review was to assess the risks and benefits of bisphosphonate therapy in terms of clinical outcome and complications in patients with PDB. A secondary aim was to investigate the effects of bisphosphonates on markers of bone turnover.

3.3 Methods

3.3.1 Criteria for Considering Studies for This Review

3.3.1.1 Types of Studies

Only RCTs comparing bisphosphonates versus placebo or other active treatments for Paget's disease of bone in adults, including those which compared regimens of

bisphosphonates which aimed to normalise biochemical markers of bone turnover with those that did not, were included.

3.3.1.2 Types of Participants

Patients aged 18 years and over with PDB confirmed by plain radiographs or isotope bone scintigraphy. [3]

3.3.1.3 Types of Interventions

The experimental intervention was defined as the use of bisphosphonates including simple bisphosphonates (etidronate, clodronate, or tiludronate) or aminobisphosphonates (alendronate, neridronate, pamidronate, olpadronate, ibandronate, risedronate, or zoledronate).

The comparator interventions were defined as placebo or other types of intervention including calcitonin, comparisons between simple bisphosphonates and aminobisphosphonates; comparisons between two different aminobisphophonates, or comparisons between different treatment strategies using bisphosphonates.

The following comparisons were made:

a. bisphosphonates versus placebo;
b. bisphosphonates versus calcitonin;
c. comparison between two bisphosphonates:
d. comparison between simple bisphosphonates;
e. comparison between aminobisphosphonates and simple bisphosphonates;
f. comparison between different aminobisphosphonates;
g. comparison between bisphosphonate regimens which aimed to normalise elevated bone turnover with those that did not (intensive versus non-intensive treatment).
h. comparison between bisphosphonates versus bisphosphonates plus calcitonin.

Calcium and/or vitamin D supplementation and pain-killers were considered as co-

interventions, if their use was equally available to the two treatment groups. The planned analysis according to time points (three or six months from the start of treatment; one, two, three, four or more years from the start of treatment; and at the end of the trial) were not performed as nearly all the trials had only a 6 month follow-up period.

3.3.1.4 Types of Outcome Measures

Major outcomes

The following patient-oriented evidence was included.

- Change in pain:
    a. Studies reporting any of the following tools for measuring pain: visual analogue scales, nominal scales and/or pain domains in generic quality of life measures (e.g. 'Bodily Pain' in SF-36);
    b. Only evaluations of pain rated by the patient (physician-rated evaluations were excluded);
    c. Change in pain measured as a continuous variable whenever possible. Whenever pain was assessed as the number of patients with improved bone pain from baseline, the following categories were considered:
        i. complete reduction of pain (reduction from baseline is 100%);
        ii. complete/partial reduction of pain (reduction from baseline is greater or equal to 50%, up to and including complete reduction);
        iii. any reduction in pain.
- Number of patients experiencing side effects related to use of bisphosphonates specifically symptomatic hypocalcaemia, oesophagitis, osteonecrosis of the jaw, uveitis, arrhythmias, atypical fracture, renal failure and influenza-like symptoms. Influenza-like symptoms included myalgia, pyrexia, nausea, diarrhoea, dyspepsia, abdominal pain, headache, bone pain, fatigue.

- Number of patients experiencing radiologically confirmed clinical fractures.
- Number of patients who received orthopaedic surgery.
- Change in quality of life:
    a. Studies reporting any of the following tools for measuring generic quality of life e.g. Medical Outcome Study (MOS) [78], SF-36, EuroQOL five dimensions questionnaire (EQ-5D), or tools for measuring arthritis-specific quality of life e.g. arthritis-specific version of the SF-36, Stanford HAQ Disability Index, were included;
    b. Change in quality of life was measured as a continuous variable whenever possible. Whenever quality of life was assessed as the number of patients with improved quality of life from baseline, any improvement in quality of life was considered.
- Change in hearing thresholds or degree of deafness:
    a. Studies reporting audiometric assessment and hearing threshold examinations;
    b. Change in hearing thresholds or degree of deafness measured as a continuous variable whenever possible;
    c. The number of patients receiving a hearing aid as an assessment of degree of deafness was considered.
- Number of patients withdrawing due to adverse events.

Minor outcomes

For patient-oriented evidence, the number of patients that experienced pain was considered. For disease-oriented evidence, the following were included: (I) mean percentage change from baseline in serum total ALP activity. The number of patients who normalized their ALP level was also recorded; and (II) number of patients that relapsed due to recurrence of an increased ALP level.

3.3.2 Search Methods for Identification of Studies

3.3.2.1 Electronic Searches

Electronic searches in the following databases were performed:

a. MEDLINE (1946 to present);
b. EMBASE (1980 to present);
c. The Cochrane Central Register of Controlled Trials (CENTRAL) (current issue);
d. ISI Web of Knowledge (all years to present).

For MEDLINE, the 'Cochrane Highly Sensitive Search Strategy' was used for identifying randomised trials in MEDLINE: sensitivity-maximizing version (2008 revision) and the Ovid format for identifying randomised trials as proposed in the *Cochrane Handbook for Systematic Reviews of Interventions.* [79] For EMBASE, a combination of the search filters for identifying randomised trials listed in the *Cochrane Handbook for Systematic Reviews of Interventions* was used. [79] No year, language or country restrictions were set.

3.3.2.2 Searching Other Resources

The reference lists of all included articles were screened to find other additional eligible studies. Specifically identified systematic reviews and meta-analyses and reference lists from identified RCTs were reviewed to identify further relevant studies. The *meta*Register of Controlled Trials (*m*RCT) (http://www.controlled-trials.com/mrct/) was searched to identify any ongoing trials. In addition, abstracts presented during the period between 2010-2015 at scientific meetings from the following societies were manually checked and those with sufficient information in the body of the abstract were included:

a. American Society for Bone and Mineral Research;
b. International Bone & Mineral Society ;
c. International Osteoporosis Foundation/European Society for Clinical

and Economic Aspects of Osteoporosis and Osteoarthritis;

d. European Calcified Tissue Society

3.3.3 Data Collection and Analysis

3.3.3.1 Selection of Studies

Two review authors (AT and LCG) independently read the results from searches on electronic databases to identify all relevant articles based on title or title and abstract. The full manuscripts of the selected articles were retrieved for further assessment. The two authors screened the selected articles independently against the inclusion criteria. Any differences in opinion were resolved during the study selection process by discussion/consensus, or by consulting the third review author (SHR) if needed.

3.3.3.2 Data Extraction and Management

For the included articles, two authors (AT, LCG) extracted relevant data using a pre-defined data collection form designed according to guidelines from the *Cochrane Handbook for Systematic Reviews of Interventions.* [79] The following data was extracted:

a. Study identification: author, year of publication, journal.
b. Characteristics of the trial: study design, calculation of sample size before the study, use of intention to treat analysis, setting/location, number of centres, country, period of study, follow-up period, outcomes, method of randomisation, allocation concealment and blinding.
c. Inclusion and exclusion criteria.
d. Characteristics of participants: age, gender, whether or not patients had monostotic disease, patients treated previously for Paget's disease of bone, symptomatic patients, numbers randomised, numbers excluded (post-randomisation), reasons for exclusion, participants

assessed, withdrawals and reasons for withdrawal.

e. Characteristic of intervention: drug analysed, comparator, dosage, duration of treatment, co-interventions.
f. Risk of bias assessment.
g. Outcome data (Types of outcome measures).
h. Source of funding.
i. Conflict(s) of interest.

A specific database to carry out the data extraction process was created. Any differences of opinion during the data extraction process were resolved by discussion/consensus by AT and LCG and occasionally by discussion with the third author (SHR).

When data were neither available from the text of the original manuscript, nor available after requests made to the relevant authors, they were directly extracted from figures shown in the manuscript by using a vector graphics editor.

3.3.3.3 Assessment of Risk of Bias in Included Studies

Two authors (AT, LCG) assessed the risk of bias in included studies independently as recommended by the *Cochrane Handbook for Systematic Reviews of Interventions*. [79] The following methodological domains were assessed.

a. Adequate sequence generation (checking for possible selection bias): if the methods used to generate the allocation sequence for each included study were in sufficient detail to allow an assessment of whether it should produce comparable groups.
b. Adequate measures to conceal allocation (checking for possible selection bias): if the method used to conceal the allocation sequence for each included study was in sufficient detail to determine if intervention allocation could have been foreseen in advance of, or during recruitment, or changed after assignment.
c. Blinding of study participants and study researchers (checking for possible

performance bias): all the methods used, if any, to blind participants and study researchers from knowledge of which intervention a participant received for each included study.

d. Blinding of outcome assessors (checking for possible detection bias): all the methods used, if any, to blind outcome assessors from knowledge of which intervention a participant received for each included study.
e. Incomplete outcome data (checking for possible attrition bias through withdrawals, drop-outs, protocol deviations): the completeness of data including attrition and exclusions from the analysis. Any reported attrition and exclusions were stated. The numbers included in the analysis at each stage (compared with the total randomised participants); reasons for attrition or exclusion where reported; and whether missing data were balanced across groups or were related to outcomes. A high attrition rate was not considered a source of bias if an Intention-to-treat (ITT) analysis was performed. Where sufficient information was reported or could be supplied by the study authors, missing data was re-included in the analyses that were undertaken.
f. Selective outcome reporting (checking for possible reporting bias): differences, if any, between the planned protocol analysis data and the reported data for each included study, to look for unreported findings.
g. Other potential threats to validity (considering external validity, e.g. relevant use of co-intervention).

Each of these criteria was explicitly judged as "Low risk", "High risk" or "Unclear risk" of bias.

The likely overall magnitude of the bias for each included study and whether it was likely to impact on the findings was assessed. A summary assessment of the risk of bias for each outcome was generated. In order to assess the risk of bias within a study, adequate sequence generation, allocation sequence concealment and incomplete outcome data as key domains for all the outcomes were evaluated. Blinding of study participants and study researchers as key domains for change in

pain, reporting of adverse events and change in quality of life were evaluated. Blinding as a key domain for assessing the risk of bias for fractures, receiving orthopaedic surgery, change in hearing thresholds and total alkaline phosphate activity was not considered. Other potential threats to validity included the relevant use of painkillers as co-interventions, which were considered a key domain for change in pain and change in quality of life.

For each outcome, low risk of bias across studies was considered when most information originated from studies at low risk. High risk of bias across studies was considered when the proportion of information from studies at high risk of bias was sufficient to affect the interpretation of results. Lastly, unclear risk of bias was judged when most information was from studies at unclear risk of bias.

Any differences of opinion during the assessment of risk of bias process were resolved through discussion and consensus. For disagreements not resolved by consensus, the third review author (SHR) was consulted.

3.3.3.4 Measures of Treatment Effect

For dichotomous outcomes, the effect of treatment across trials was estimated using the Risk Ratio (RR) with the corresponding 95% CI. For significant outcomes, the number needed to treat (NNT) to benefit one patient or the number needed to harm (NNH) one patient as the inverse of the pooled Risk Differences (RDs) was computed.

Dichotomous outcomes were as follows:

a. number of patients who experienced side effects;
b. number of patients who experienced radiologically confirmed clinical fractures;
c. number of patients who received orthopaedic surgery;
d. number of patients who withdrew due to adverse events;
e. number of patients who relapsed due to recurrence of bone pain;
f. number of patients who relapsed due to recurrence of increased serum

alkaline phosphatase level.

Where continuous scales of measurement were used to assess the effects of treatment, the Mean Difference (MD) with the corresponding 95% CIs was used. If different scales were used to measure an outcome, the Standardised Mean Difference (SMD), as an expression of the size of the intervention effect in each study relative to the variability observed in that study, was calculated. [79]

$$\text{SMD} = \frac{\text{Difference in mean outcome between groups}}{\text{Standard deviation of outcome among participants}}.$$

Continuous outcomes were as follows:

a. Change in pain;
b. Change in quality of life;
c. Change in hearing thresholds;
d. Mean percentage change from baseline in serum total alkaline phosphatase activity.

3.3.3.5 Unit of Analysis Issues

The unit of analysis was individual people undergoing treatment for PDB. Only RCTs were included, and studies with non-standard designs such as cross-over trials were excluded.

For studies with more than one intervention group (such as different doses of the same bisphosphonate) data from the experimental intervention groups were combined to create a single pair-wise comparison versus the control group.

3.3.3.6 Dealing with Missing Data

When data on the outcome were not available from trials, the primary investigators of the eligible trials were contacted. The authors were contacted using email addresses given in the study publications. When no response was received, only the

available data was analysed, ignoring the missing data, as it was assumed that these data were missing at random.

A sensitivity analysis (Section 3.3.3.11) according to the missing data was performed to assess how robust the assumption that the missing data were missing at random. The potential impact of missing data of the findings of the review is addressed in the 'Discussion' section of this chapter.

3.3.3.7 Assessment of Heterogeneity

Global estimates for each variable effect were computed by conducting a meta-analysis of the single effect measure of the study (RR for dichotomous variables and MD or SMD for continuous variables) using the Cochrane Collaboration statistical software, Review Manager 2014. Prior to calculating estimates of effect, the presence and degree of heterogeneity was assessed by means of I^2 to describe the percentage of the variability in effect estimates that is due to heterogeneity rather than chance, based on the following formula:

$$I^2 = \left(\frac{Q - df}{Q}\right) \times 100\%$$

Where Q is the chi-squared statistic and df is its degrees of freedom. [79] An I^2 value greater than 75% was categorised as considerable heterogeneity. [79]

A narrative review of potential heterogeneity was undertaken according to the variability in populations, interventions, outcomes and settings.

3.3.3.8 Assessment of Reporting Biases

As several studies had a small sample size, the likely impact of the 'small-study effect' was assessed (the tendency for estimates of the intervention effect to be more beneficial in smaller studies) using inverted funnel plot techniques. Drawing funnel plots were planned when there were at least 10 included studies. However, none of

the comparisons had these numbers of studies, so no funnel plot was drawn.

3.3.3.9 Data Synthesis

Review Manager 2014 was used for data synthesis. Quantitative synthesis was planned if more than one eligible study was identified. Where appropriate, a pooled estimate of treatment effect across similar studies for each pre-specified outcome was calculated. The overall effect by meta-analysis was estimated using a random-effect model. Meta-analysis was not conducted if there was considerable heterogeneity (I^2 more than 75%) [6]. RRs and 95% CIs for dichotomous data were calculated. The NNT was calculated to provide an indication for each dichotomous outcome, reflecting the number of patients required to obtain a beneficial outcome with the intervention. For continuous data measured in the same scale, MDs were calculated. When different scales were used, SMDs were calculated. Where possible, data were analysed using an ITT model.

The mean and standard deviation was used when available. If only median and interquartile ranges were reported, guidance from the *Cochrane Handbook for Systematic Reviews of Interventions* was followed [79], where the median was used as the mean and the standard deviation was set as 1.35. If no standard deviation was given at the end of the study, the baseline standard deviation was used at the end as well.

A narrative review of eligible studies was undertaken where statistical synthesis of data from more than one study was not possible or appropriate.

3.3.3.10 Subgroup Analysis and Investigation of Heterogeneity

None of the two planned subgroup analysis [symptomatic (bone pain) versus asymptomatic patients; biochemically active (raised alkaline phosphatase) PDB versus non-biochemically active PDB (normal ALP)] were performed because there was insufficient data to allow for these analyses to be performed.

3.3.3.11 Sensitivity Analysis

The following sensitivity analysis was performed:

a. To determine the robustness of the pooled effect estimate in terms of risk of bias by including or excluding studies with high or unclear risk of bias from the comparative analysis.
b. To determine the robustness of the pooled effect estimate in terms of missing data by including or excluding studies with high levels of missing data, more than 20% of missing data for the overall trial population, or for any of the trial arms from the comparative analysis.
c. To determine the robustness of the pooled effect estimate in terms of withdrawals by performing either the "worst case" scenario sensitivity analysis (all the withdrawals data as negative events) or the "same as control" scenario sensitivity analysis, where the rate of negative events in the withdrawals data were the same as in the control group.

3.3.3.12 'Summary of Findings' Table

The quality of the evidence was evaluated using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach and from this, a 'Summary of findings' table was produced. [80] This table contains the following three elements:

a. The outcomes most relevant to patients (critical and important outcomes according to GRADE);
b. A summary measure for the quality of the evidence (confidence in estimate of a treatment effect);
c. A summary estimate for the RR and absolute effect for the interventions of interest.

The seven important outcomes that were considered for the 'Summary of findings' table are as follows:

a. number of patients with a change in bone pain;

b. number of patients who experienced severe side effects related to use of aminobisphosphonates;
c. number of patients who experienced fractures;
d. number of patients who needed orthopaedic surgery;
e. number of patients with a change in quality of life measures including bodily pain;
f. number of patients with a change in hearing thresholds;
g. number of patients who withdrew due to adverse events.

The GRADEprofiler software was used to create the 'Summary of findings' table. [81]

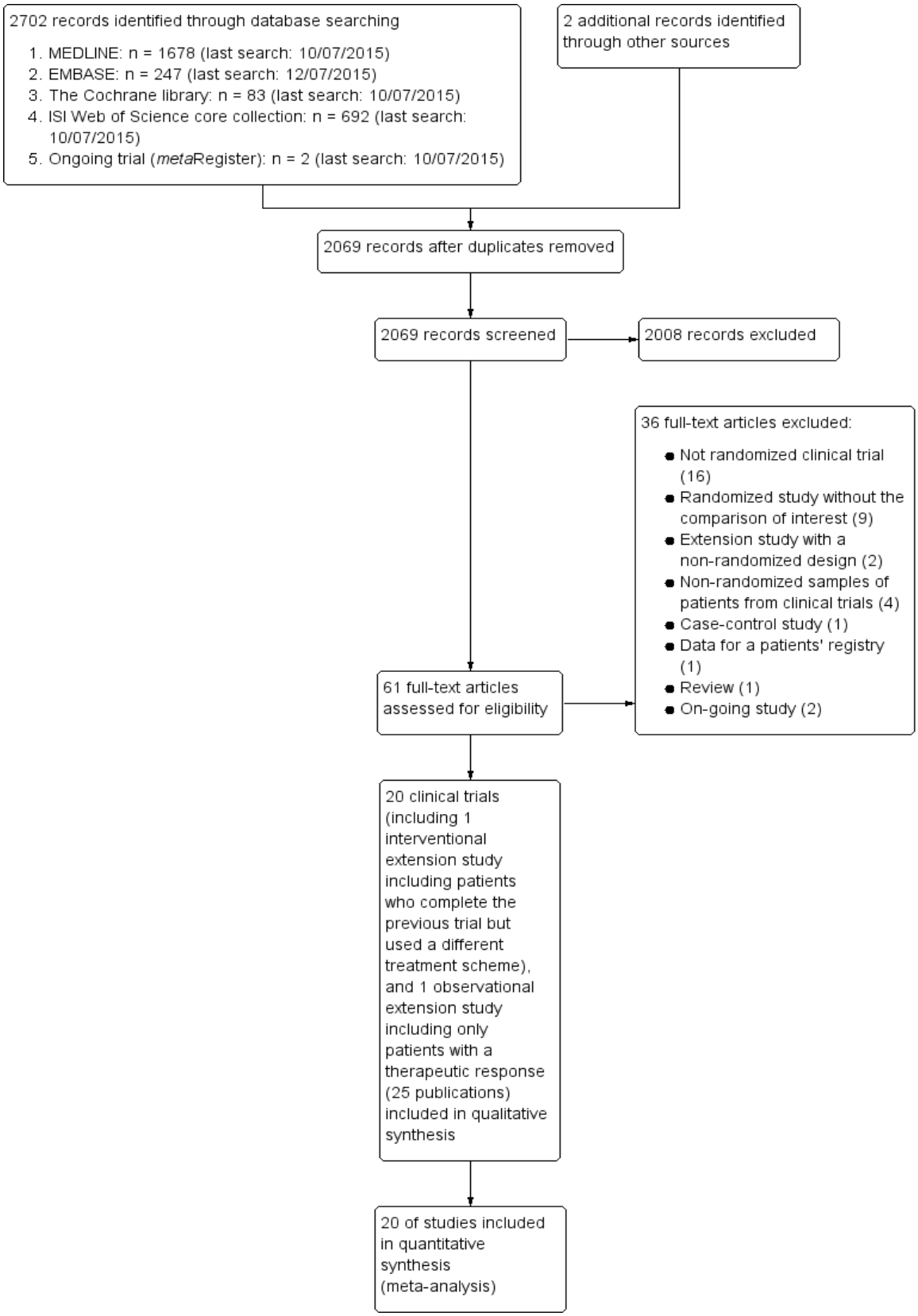
3.4 Results

3.4.1 Quantity of Research Available

The literature search revealed 2702 citations as depicted in Figure 3.1. Of these, 61 articles were retrieved for further review. A total of 36 articles were excluded for various reasons, including 16 non-randomised clinical trials [71, 82-96], 9 randomised clinical trials without the comparison of interest [97-105], 2 extension studies with a non-randomised design [106, 107], 4 clinical trials with non-randomized samples of patients [108-111], 1 case control study [112] 1 data for a patients' registry [113], 1 review [114] and 2 on-going trials. [115, 116]

In total, 20 trials (25 references) met the selection criteria for inclusion in this report. [29, 35, 36, 72, 75, 76, 117-134] All the included articles were published in English.

Figure 3.1: Flow diagram of the systematic review process



Qualitative synthesis is the process of collecting relevant data from individual studies and quantitative synthesis is the numerical and statistical comparison of data across studies

3.4.2 Inconsistent or Missing Information

Most of the study authors were contacted to request additional information or clarify inconsistencies that might have been found across publications and the outcome of this process is summarised in Table 3.1.

Table 3.1: Survey of authors' reactions to information requests

Study ID	Study author contacted	Study author replied	Additional data provided
Altman [117]	No	-	Not applicable
Barreira [118, 119]	01/12/2014	No	Not applicable
Buckler [120], Schaffer [121]	30/06/2016	No	Not applicable
Canfield [122]	No	-	Not applicable
Fraser [123]	30/6/2014	No	Not applicable
Langston [36], Ralston [128]	30/6/2014	29/12/2014	Provided more information on co-interventions and blinding (Ralston 1987, Langston 2010), data on pain, QoL, hearing and mean ALP and SD change (Langston 2010).
McClung [124]	30/6/2014	02/07/2014	Original study data no longer accessible
Merlotti [125]	30/6/2014	No	Not applicable
Miller [75]	30/6/2014	No	Not applicable
O'Doherty [126]	30/6/2014	No	Not applicable
O'Donoghue [127]	No	-	Not applicable
Reginster [129]	30/06/2014	30/06/2014	Original study data no longer accessible
Reid [29, 35, 72, 130]	30/6/2014	02/09/2014	Provided more information on concealment (Reid 1996, 2004), mean ALP and SD change (Reid 2004), blinding (Reid 2005) and data on adverse events (Reid 2004).
Roux [132]	30/6/2014	08/07/2014	Original study data no longer accessible
Siris [76]	30/06/2014	01/07/2014	Original study data no longer accessible
Tan [133]	28/02/2015	22/06/2015	Unpublished data provided
Walsh [134]	30/6/2014	19/08/2014	Provided more information on concealment, mean ALP and SD change, data on pain scores, QoL and adverse events.

3.4.3 Characteristics of Included Studies

Ten studies compared bisphosphonates vs. placebo including a total of 801 patients [29, 72, 117, 120, 122-124, 126, 128, 129], one compared two non amino-bisphosphonates including a total of 234 patients [132], 2 compared non amino-bisphosphonates vs. aminobisphosphonates including a total of 212 patients [75, 76], four compared two amino-bisphosphonates including a total of 546 patients [118, 119, 125, 130, 134], one compared etidronate vs. etidronate plus calcitonin including a total of 44 patients [127] and one compared intensive treatment (aimed at normalising ALP) vs. symptomatic treatment (aimed at treating bone pain) including a total of 1331 patients. [36] An extension to this study which included 502 patients [133] investigated the effects of these treatment strategies for up to 7.3 years. Although the authors defined the study as an extension study, it was not an observational extension study, but an interventional extension study where the participants continued intensive or symptomatic treatment as in the preceding study. In this case, zoledronate was used as the treatment of first choice in the extension as compared with risedronate in the PRISM study. In another extension [35,131] of an original study by Reid and colleagues [130], only patients whose ALP was normal at the end of the core study were selected to continue with follow-up.

The sample sizes of included studies ranged from 15 to 1331, and eleven studies had less than 100 patients. Only the PRISM trial [36] had more than 1,000 patients. Sample size calculations were performed in advance of the study for only five trials. [36, 120, 130, 132, 134]

The patient populations were reasonably homogeneous in terms of age and gender of the subjects. A summary of the principal characteristics of the trial samples is shown in Table 3.2. The mean age ranged from 66 to 76 years, the percentage of males ranged from 51 to 74%, and the percentage of symptomatic patients from 63% to 100%. Nearly all the patients had a raised serum total ALP but one study [36] included patients with normal ALP at baseline (707/1324; 53%). ALP was normal at baseline in patients who were enrolled into an extension of this study (337/502; 67%).

[133] The percentage of symptomatic patients (defined as patients with pain due to PDB bone lesions) ranged from 63 to 100%, although this information was not recorded for about half of the studies.

For all but one study [36] and its extension [133] the primary outcome was the change in serum total ALP activity. Most of the studies did not include the major outcomes (bone fractures, need of orthopaedic surgery, changes in QoL or hearing thresholds) of primary interest in this review.

Thirteen studies had only six months of follow up and two studies [120, 128] had only three months. Another three studies [75, 127, 134] had 12 months of follow up. The PRISM study of intensive vs. symptomatic treatment study [36] was an event driven trial with an average of 4.3 years follow up (range 2-5 years). An extension to the PRISM trial [133] followed patients up for an additional three years giving a total of 7.3 years of follow up data. An extension to the comparison of zoledronate and risedronate [35] followed patients for up to 6.5 years but these were a selected group that had normalised ALP during the core study.

Table 3.2: Summary of principal characteristics of included studies

Study ID	Intervention	Comparator	ALP	Follow-up	n	Age	Male	Symptomatic	Previously Treated
Altman [117]	Etidronate	Placebo	Yes	6m	50	67y	60%	NA	NA
Canfield [122]	Etidronate	Placebo	Yes	6m	48	NA	58%	NA	NA
Ralston [128]	Etidronate	Placebo	No	3m	32	NA	NA	100%	38%
Fraser [123]	Tiludronate	Placebo	Yes	18m	112	70y	54%	63%	NA
McClung [124]	Tiludronate	Placebo	Yes	6m	139	70y	54%	NA	NA
Reginster [129]	Tiludronate	Placebo	Yes	6m	149	69y	54%	NA	82%
O'Doherty [126]	Alendronate	Placebo	Yes	6m	15	67y	60%	87%	66%
Reid [72]	Alendronate	Placebo	Yes	6m	55	70y	56%	NA	35%
Buckler [120]	Zoledronate	Placebo	Yes	3m	176	71y	61%	NA	NA
Reid [29]	Ibandronate	Placebo	Yes	6m	25	73y	74%	NA	64%
Roux [132]	Tiludronate	Etidronate	Yes	6m	234	69y	59%	74%	71%
Siris [76]	Alendronate	Etidronate	Yes	6m	89	69y	67%	NA	25%
Miller [75]	Risedronate	Etidronate	Yes	12m	123	66y	69%	91%	72%
Walsh [134]	Alendronate	Pamidronate	Yes	12m	72	70y	58%	94%	39%
Barreira [119]	Olpadronate	Pamidronate	Yes	6m	27	NA	NA	NA	NA
Merlotti [125]	Zoledronate	Pamidronate	Yes	6m	90	70y	69%	99%	67%
Reid [35, 130]	Zoledronate	Risedronate	Yes	6.5y	357	70y	68%	NA	54%
O'Donoghue [127]	Etidronate+ Calcitonin	Etidronate	Yes	12m	44	NA	NA	100%	10%
Langston [36]	Intensive	Symptomatic	No	4.3y	1331	74y	51%	69%	70%
Tan [133]	Intensive	Symptomatic	No	3y	502	76y	54%	28%	70%

3.4.4 Study Funding Sources

Eleven out of 21 studies were funded by the drug manufacturer. Four of these studies were funded by government agencies or charities. In three studies funded by government agencies or charities, the authors stated that the drug manufacturer supplied the study drug. Data on funding source was not mentioned or was unclear in five studies.

3.4.5 Risk of Bias in Included Studies

Figure 3.2 and Figure 3.3 provide an overview of the judgments made regarding the risk of bias in all included studies.

Figure 3.2: Risk of bias in each included study

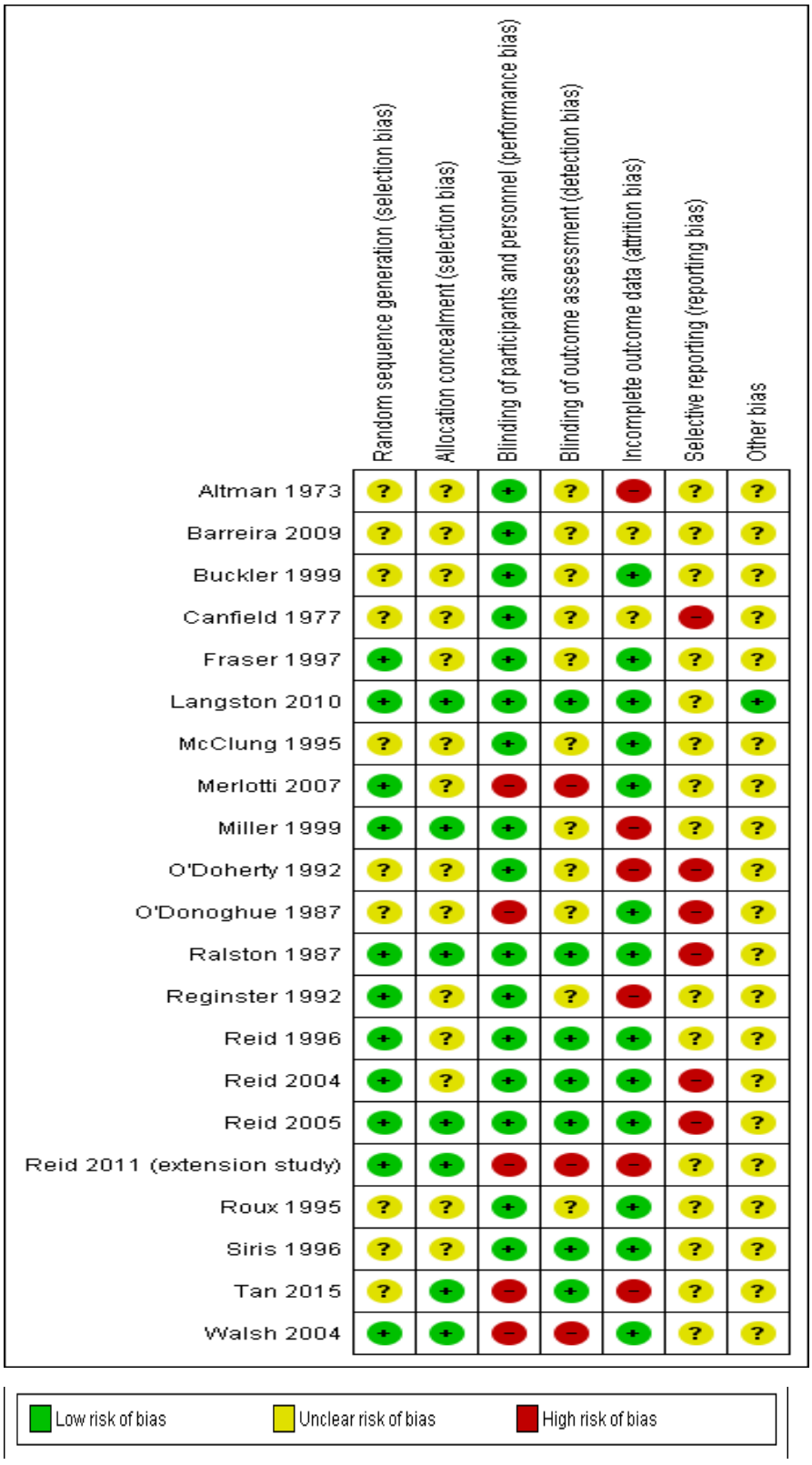
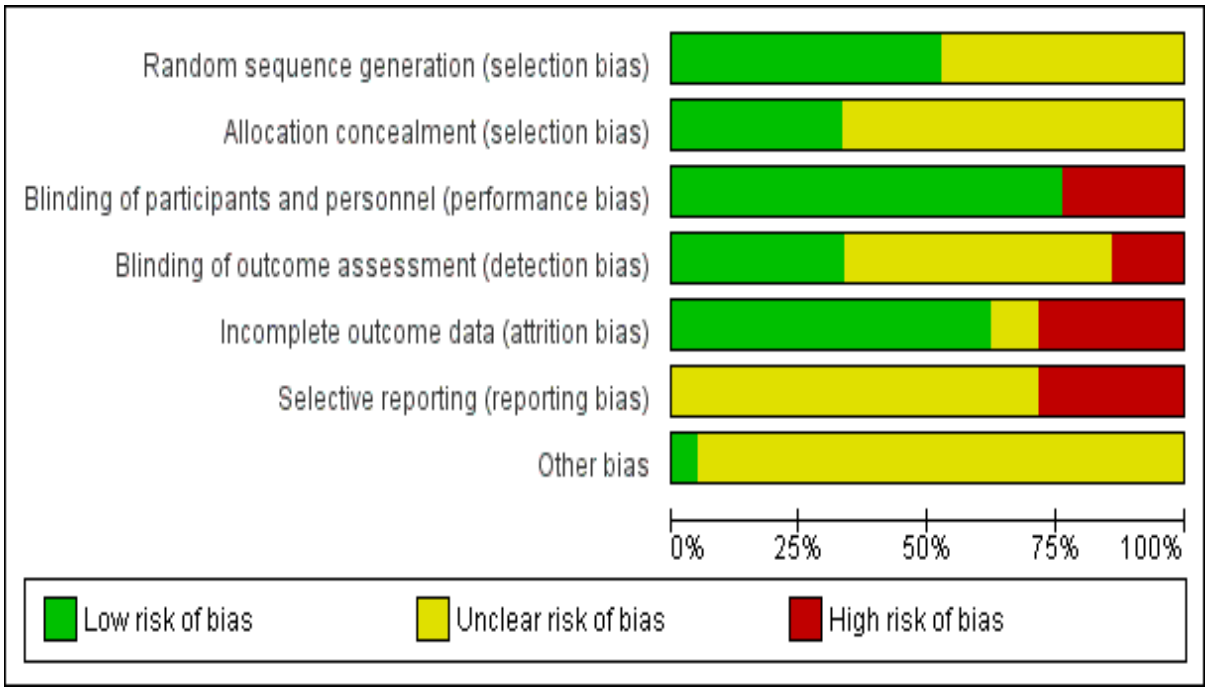


Figure 3.3: Risk of bias across all included studies



3.4.6 Allocation

The generation of the random sequence for allocation was considered adequate in half the studies. Risk of bias was judged as unclear in the rest. The allocation concealment was considered adequate in only five studies and judged as unclear in the rest. In no article was the risk of selection bias considered as high.

3.4.7 Blinding

Five studies [36, 125, 127, 133, 134] were open-label and as a result, their performance risk of bias was considered as high for subjective outcomes such as pain or QoL. The rest of the studies were double blinded. In addition, the outcome assessment was not blinded in 1 study. [75]

3.4.8 Incomplete Outcome Data

The risk of bias due to incomplete outcome data was considered low in thirteen studies. [29, 36, 72, 76, 120, 123-125, 127, 128, 130, 132, 134] Four studies were judged

to have a high risk of bias because the amount of missing data was large [129] or not appropriately handled. [75, 117, 126] For the remaining two studies the risk of bias was unclear. [119, 122]

3.4.9 Selective Reporting

Reporting bias was difficult to evaluate since the study protocol was not available for any of the studies. Five studies were judged to have a high risk of bias due to selective reporting because the data on adverse events were not clearly detailed [122], there were no data on adverse events [126, 127] or because adverse events were not systematically recorded in the trial. [29, 128] In addition, three studies were judged to have a high risk of bias due to selective reporting because details of assessment for some outcomes included in the 'results' section (pain, fractures) were not detailed in the 'methods' section. [126, 127] Conversely in another study, some outcomes mentioned in the 'methods' section (pain, fractures) were not provided in the 'results' section. [130] Risk of bias was judged as unclear for the rest of the studies.

3.4.10 Other Potential Sources of Bias

One study [36] and its extension [133] had a potential risk of bias for subjective outcomes due to its open design. In these studies the attending clinician was able to choose which bisphosphonate should be prescribed resulting in heterogeneity between groups in the number and types of bisphosphonate used, However adherence to the randomised treatment strategy was confirmed by the fact that ALP values were significantly lower in the intensive group as compared with the symptomatic group for both trials.

3.4.11 Reporting Bias

Funnel plots were planned to explore the risk of reporting bias for all analysed outcomes but were not made, as for all the outcomes the number of included studies were too low.

3.4.12 Effects of Interventions

Table 3.3 provides a summary of the effects of bisphosphonates compared with placebo across all included studies. (The GRADE Working Group grades of evidence are provided in Table 3.4. The basis for the assumed risk (the median control group risk across studies) is provided in the footnotes under Table 3.3. The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

Table 3.3: Summary of the effects of bisphosphonates compared with placebo

Outcomes	**Illustrative comparative risks* (95% CI)**		**Relative effect (95% CI)**	**Number of Participants (studies)**	**Quality of the evidence (GRADE)**	**Comments**
	Assumed risk	**Corresponding risk**				
	Placebo	**Bisphosphonates**				
Number of patients with change in bone pain Visual analogue scale[1] Follow-up: mean 6 months	**227 per 1000**	**446 per 1000** (292 to 682)	**RR 1.97** (1.29 to 3.01)	481 (7 studies)	⨁⨁⨁⊖ **moderate**[2]	When bone pain was assessed as a continuous variable (3 studies), results were not homogeneous (2 studies show no differences).
Number of patients who experienced fractures radiologically confirmed Follow-up: mean 6 months	**0 per 1000**	**7 per 1000** (2 to 27)	**RR 0.89** (0.18 to 4.31)	356 (4 studies)	⨁⊖⊖⊖ **very low**[3,4,5]	There were no fractures in the placebo group. Assumed risk not calculable.
Number of patients who needed orthopaedic surgery - not measured	See comment	See comment	Not estimable	-	See comment	Effect is uncertain
Number of patients with change in quality of life measures - not measured	See comment	See comment	Not estimable	-	See comment	Effect is uncertain

Number of patients with change in hearing thresholds - not measured	See comment	See comment	Not estimable	-	See comment	Effect is uncertain
Number of patients who experienced side effects related to use of bisphosphonates Follow-up: mean 6 months	**483 per 1000**	**638 per 1000** (440 to 928)	**RR 1.32** (0.91 to 1.92)	678 (6 studies)	⨁⊖⊖ **low**[6,7]	Gastrointestinal side effects (diarrhoea, dyspepsia, vomiting, nausea, oesophagitis or gastritis) were the most common.
Number of patients who withdrew due to adverse events Follow-up: mean 6 months	**41 per 1000**	**41 per 1000** (17 to 102)	**RR 1.01** (0.41 to 2.52)	517 (6 studies)	⨁⨁⊖ **moderate**[8,9]	

[1] Visual analogue scale ranging from 0 to 10 was used in four of the seven studies. One study classified pain in three groups and the tool used for pain assessment was not detailed in the other two studies.

[2] Downgraded by one level. High risk for attrition bias in 3 studies and high risk for reporting bias in 3 studies. Outcome did not change in a sensitivity analysis excluding high risk studies.

[3] Downgraded by two levels. Most information was from studies at high risk of bias. High risk for attrition bias in 2 studies and high risk for reporting bias in 1 study.

[4] Downgraded by one level (indirectness). Long-term impact on fractures was not assessed.

[5] Downgraded by one level (imprecision). Low number of events, resulting in wide CI.

[6] Donwgraded by one level. High risk for attrition bias in two studies.

[7] Downgraded by one level (inconsistency). The type of side effects considered was heterogeneous within studies. In addition, considerable heterogeneity was shown when meta-analysing the six studies (I^2= 75%, P = 0.001). However, only one study showed more adverse events in the placebo group than in bisphosphonates group. A sensitivity analysis without this study had anI^2= 6% with a RR 1.38 (1.08-1.78).

[8] Downgraded by one level. Half of the studies at high risk of bias. High risk for attrition bias in three studies and high risk for reporting bias in one study.

[9] Although there were a low number of events, resulting in a wide CI, the outcome was not downgraded as RR was near 1.

Table 3.4: GRADE Working Group grades of evidence

Grade	Description
High Quality	Further research is very unlikely to change our confidence in the estimate of effect.
Moderate Quality	Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low Quality	Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very Low Quality	Very uncertain about the estimate.

3.4.13 Major Outcomes

3.4.13.1 Effect on Bone Pain

Bone pain was not considered as primary outcome in any of the studies, although fourteen of the twenty studies reported changes in bone pain as a secondary outcome. Pain was assessed by a visual analogue scale ranging from 0 to 10 in eight of the fourteen studies. [76, 123, 124, 128, 129, 130, 132, 134] Three studies used SF-36 bodily pain. [36, 75, 133] The tool used for pain assessment was not detailed in the other three studies. [122, 126, 127]

When bisphosphonates were compared with placebo, the overall effect over total or partial pain relief was favourable to bisphosphonates with a RR of 1.97 (1.29 to 3.01), NNT 5 (2-15). Results were consistent across the trials, as all the studies included in the meta-analysis showed a favourable effect (RR range from 1.20 to 10.00) as

demonstrated in Figure 3.4. However, when change in bone pain was assessed as a continuous variable, data were heterogeneous. Etidronate was better than placebo in one study [128], but there were no differences between bisphosphonates and placebo in average pain scores in two other studies comparing tiludronate or alendronate respectively. [72, 124] (Figure 3.5).

Figure 3.4: Number of patients with change in bone pain

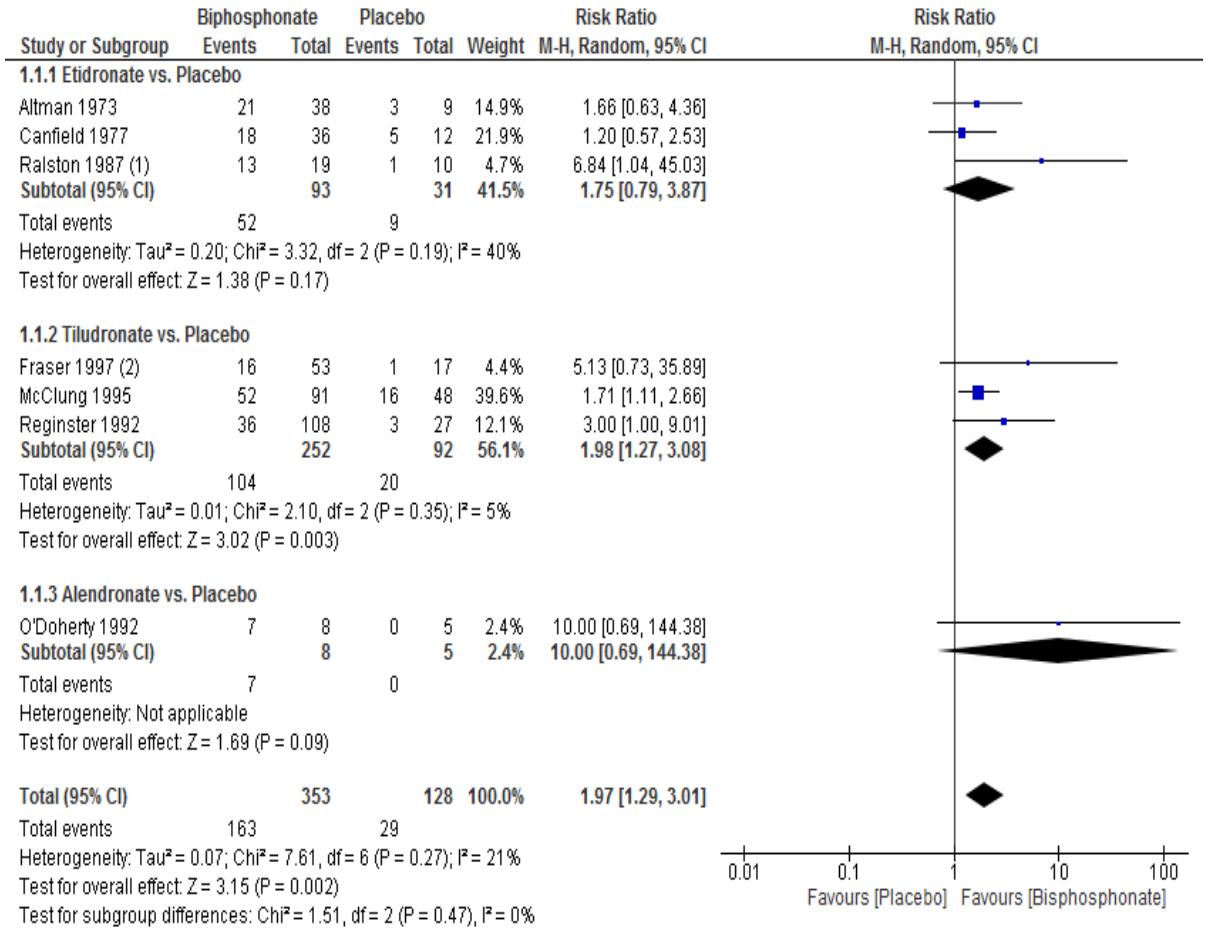
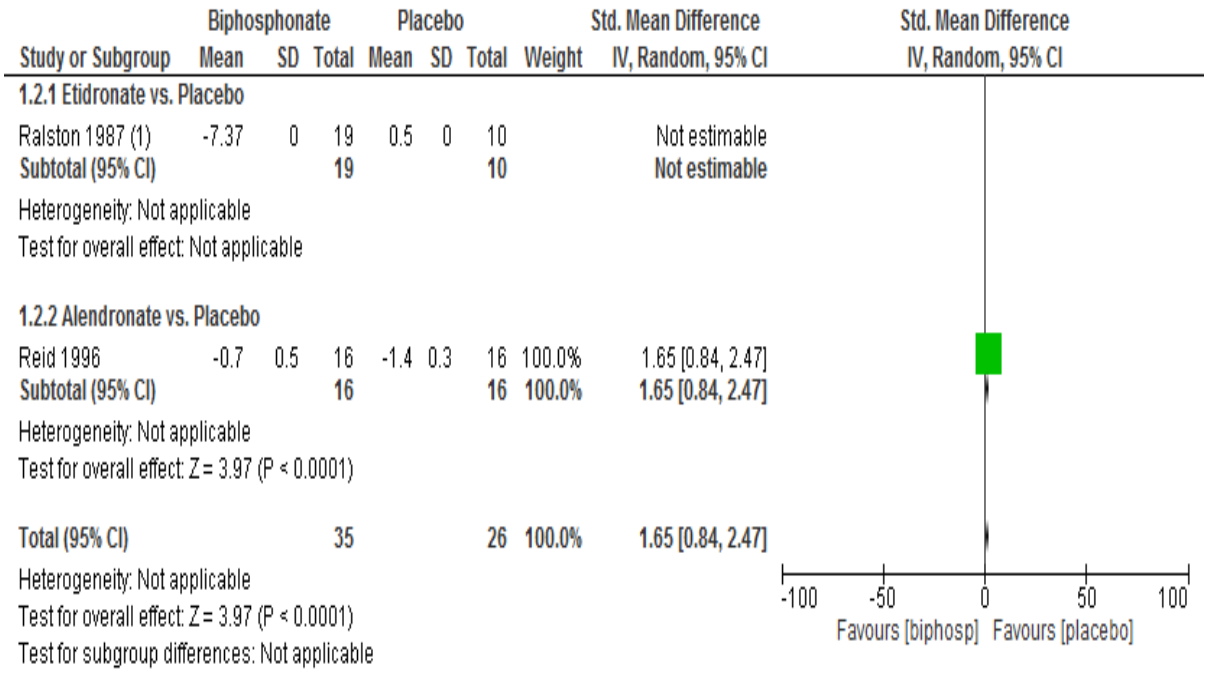
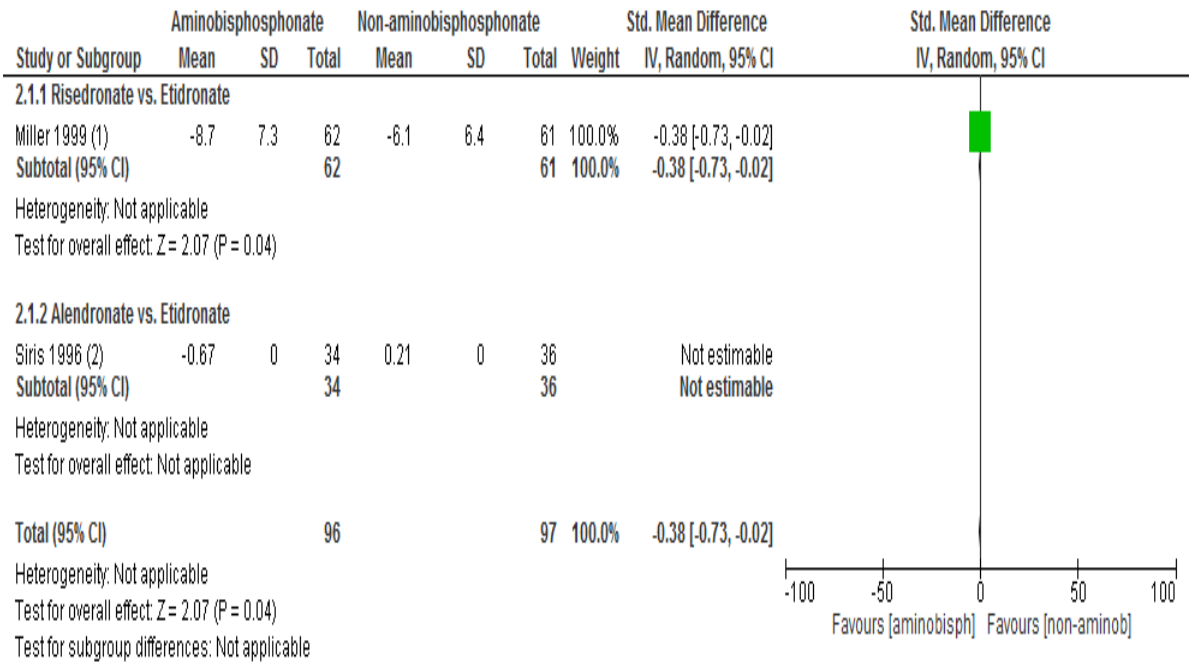


Figure 3.5: Mean change in pain from baseline between bisphosphonate and placebo



There were no differences in pain scores when etidronate was compared with risedronate [75] or alendronate. [76] (Figure 3.6). Pain assessment as a dichotomous variable was not made for this comparison.

Figure 3.6: Mean change in pain from baseline between bisphosphonates

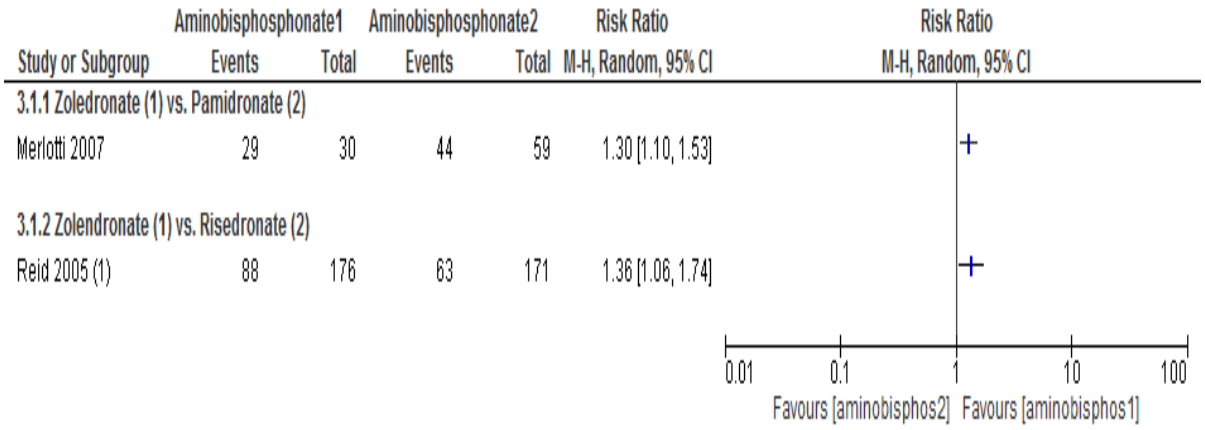


Zoledronate showed a better effect for partial or total pain relief (binary outcome) when compared with the other amino-bisphosphonatespamidronate [125] and risedronate [130] with a RR of 1.31 (1.15-1.51), NNT 7 (4-14) as shown in Figure 3.7. However, there were no differences when bone pain was assessed as a continuous outcome (scores) between zoledronate and risedronate. [130] There was no significant difference between treatments on pagetic bone pain, pagetic joint pain, or non-pagetic pain when alendronate was compared with pamidronate [134]. In this study, scores for bone pain, joint pain, and non-pagetic pain all fell significantly ($P < 0.05$) from baseline during the first 12 months of the study in both treatment groups. In the PRISM trial, and its extension [133] there were no differences in partial or total pain or in change in bodily pain measured with SF 36 between the symptomatic

andintensive treatment groups.

Lastly, the addition of calcitonin to etidronate [127] reduced the proportion of patients with partial or total pain relief [RR 0.73 (0.43-1.25)].

Figure 3.7: Number of patients with change in bone pain between amino-bisphosphonates

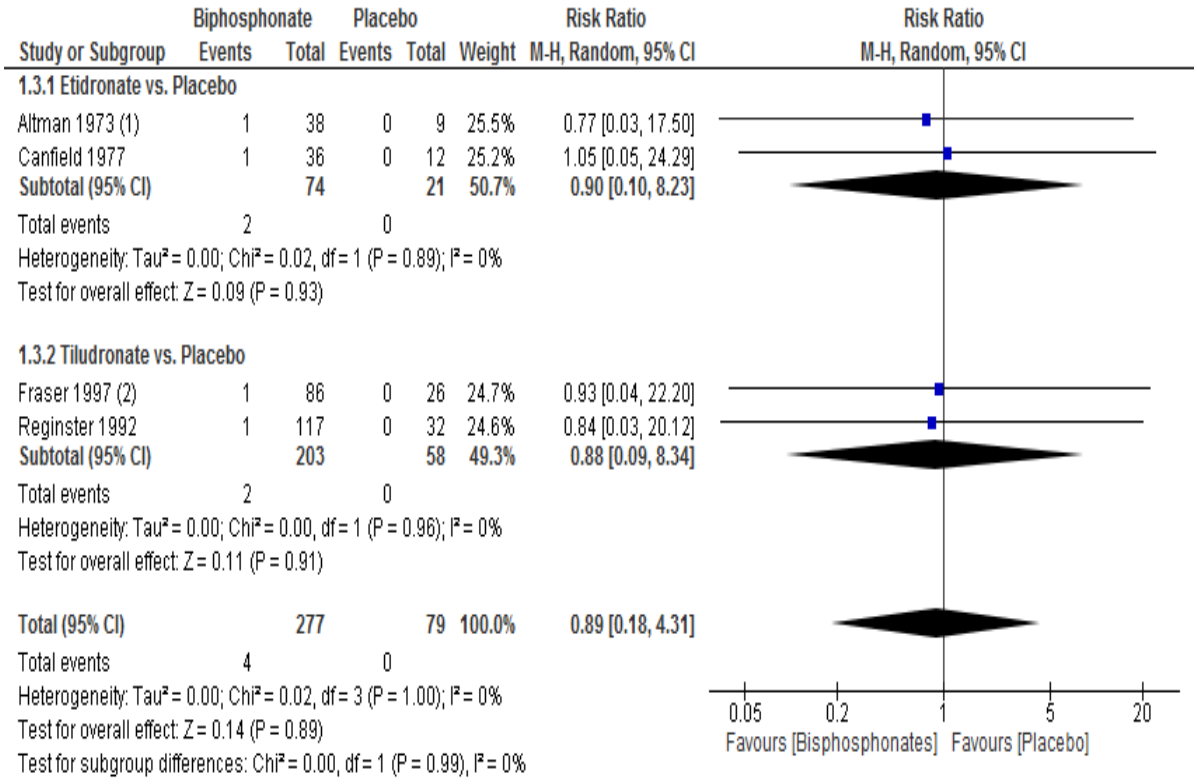


3.4.13.2 Effect on Fractures

A radiologically confirmed clinical fracture was the primary outcome in one study [36] and its extension [133], and was included as a secondary outcome in six other studies [117, 122, 123, 129, 130, 132]. The number of new fractures was extremely low in all the studies except one study [36] and its extension. [133]

There were no differences in the number of fractures when etidronate [117, 122] or tiludronate [123, 129] was compared with placebo [RR 0.89 (0.18-4.31)] as shown in Figure 3.8. The mean follow-up period of these four studies was six months. Long-term impact on fractures was not assessed.

Figure 3.8: Number of patients experiencing radiologically confirmed clinical fractures



Within bisphosphonates, tiludronate was compared with etidronate [132] and zoledronate with risedronate [130] with no differences between the different bisphosphonates (Table 3.5 and Table 3.6 respectively). As in the comparison against placebo, long-term impact on fractures was not assessed.

Lastly, the intensive vs. symptomatic treatment [36] showed no differences in the number of new fractures between the two treatment approaches: 6.96% vs. 7.39%, RR 0.94 (0.64-1.39) In this study follow-up was long enough to assess long-term impact on fractures (three years mean follow-up). In the extension to this study [133] fractures were more common in the intensive group [8.1% vs 5.2%, RR 1.90 (0.91-3.98)] but the difference between groups was not significant.

Table 3.5: The effects of tiludronate compared with etidronate

Outcome	Tiludronate		Etidronate		RR (95% IC)
	Events	n	Events	n	
Number of patients with change in bone pain	32	120	10	52	1.39 (0.74-2.61)
Number of patients who experienced a radiologically confirmed fracture	1	155	2	79	0.25 (0.02-2.77)
Number of patients who experienced severe side effect(s)	75	155	27	79	1.42 (1.00-2.00)
Number of patients who withdrew due to adverse events	10	155	2	79	2.55 (0.57-11.35)
Number of patients who normalised alkaline phosphatase levels	40	155	9	79	2.27 (1.16-4.43)

Table 3.6: The effects of zoledronate compared with risedronate

Study ID	Outcome	Zoledronate		Risedronate		RR (95% IC)
		Events	n	Events	n	
Reid [130]	Number of patients who experienced a radiologically confirmed fracture	2	177	2	172	0.97 (0.14-6.82)
Reid [35]	Number of patients who experienced a radiologically confirmed fracture	3	152	1	115	2.30 (0.24-22.36)
Reid [130]	Number of patients with change in quality of life from baseline	48	176	36	171	1.30 (0.89-1.89)
Reid [35]	Number of patients who had a clinical relapse	14	152	29	115	0.30 (0.15-0.60)
Study ID	**Outcome**	**Mean (SD)**	**n**	**Mean (SD)**	**n**	**Mean difference**
Reid [130]	Mean change from baseline in pain	-0.5 (1.75)	101	-0.4 (2.13)	92	-0.10 (-0.65-0.45)
Reid [130]	Mean change from baseline in quality of life*[1]	1.5 (0.5)	176	0.2 (0.6)	171	1.30 (1.18-1.42)
Reid [35]	Mean change from baseline in total SF-36 score*[2]	1.3 (3.1)	152	-2.5 (2.6)	115	3.8 (3.12-4.49)

3.4.13.3 Effect on the Need for Orthopaedic Surgery

The need for orthopaedic surgery was not considered as a primary outcome in any of the studies, and only one [36] study and its extension [133] included this outcome. There were no differences between intensive and symptomatic treatment, as 7.26% and 8.30% patients needed orthopaedic surgery respectively [RR 0.88 (0.60-1.27)]. In the extension to this study [133] orthopaedic procedures were more common in the intensive group: 5.6% vs 3.4%, RR 1.53 (0.63-3.72) but the difference was not significant.

3.4.13.4 Effect on QoL

The impact of bisphosphonates over QoL was not included as a primary outcome in any study. It was included as a secondary outcome in six studies but none of these compared bisphosphonates with placebo [36, 75, 125, 130, 133, 134].

There were no differences in QoL when comparing zoledronate with risedronate [130], although zoledronate showed a marginal improvement at 6 months, with a mean difference in change in physical component summary score of 1.30 (1.18-1.42). In addition, in the extension study [35], patients with a therapeutic response kept with improvement of their Total SF-36 scores until 54 months on zoledronate, but not on risedronate. For the pain domain of the SF-36, changes from baseline were significant in the zoledronate group at 24 (7.5 ± 2.6) and 36 months (5.6 ± 2.4) whereas no significant changes were observed for the risedronate group at any time point.

The general health score on SF-36 was higher when alendronate was compared to pamidronate according to the authors. [134] There were no significant differences between treatments in the other seven domains of the SF-36 or the mental and physical component summary scores. Numeric data are not shown in the manuscript.

There were no differences in QoL when risedronate was compared with etidronate

[75], or zoledronate with pamidronate. [125] In both manuscripts, the authors stated that there were no differences, but numeric data are not shown in the papers.
Lastly, there were no differences in QoL when comparing intensive vs. symptomatic treatment. [36] In the extension to this trial [133] there were similarly no differences between the groups

3.4.13.5 Effect on Deafness and Hearing Thresholds

Deafness and hearing thresholds were not considered as primary outcome in any of the studies, and only the PRISM study [36] includes these outcomes. There were no differences between intensive and symptomatic treatment; 26.73% and 27.37% patients had changes in hearing thresholds respectively [RR 0.97 (0.79-1.19)].

3.4.13.6 Side Effects

All but four trials [122, 126-128] reported side effects due to bisphosphonates. Data on side effects was heterogeneous as different side effects were recorded within studies. In addition, the assessment of the severity of side effects varied between studies. Side effects reported in trials comparing bisphosphonates vs. placebo [72, 117, 120, 123, 124, 129], bisphosphonates vs. bisphosphonates [75, 76, 119, 125, 130, 132, 134] or intensive vs. symptomatic treatment [36] are detailed in Table 3.7, Table 3.8 and Table 3.9 respectively.

Table 3.7: Summary of drug side effects reported in randomised placebo-controlled trials

Study ID	Comparison	Side Effect	Bisphosphonate	Placebo	RR (95% CI)
Altman [117]	Etidronate (38) vs placebo (9)	Diarrhoea	5 (13%)	1 (11%)	1.18 (0.16-8.93)
Buckler [120]	Zoledronate (141) vs placebo (35)	Fatigue Fever Arthralgia Pain, back Pain, skeletal Hypocalcaemia	12 (9%) 7 (5%) 15 (11%) 14 (10%) 11 (8%) 3 (2%)	0 (0%) 0 (0%) 3 (9%) 1 (3%) 2 (6%) 0 (0%)	6.34 (0.38-104.5) 3.80 (0.50-28.88) 1.24 (0.89-1.77) 3.47 (0.53-23.02) 1.37 (0.85-2.19) 1.78 (0.74-4.24)
Fraser [123]	Tiludronate (86) vs placebo (26)	Nausea Vomiting Dyspepsia Diarrhoea Arthralgia Skeletal pain Raised liver enzymes Eosinophilia	15 (17%) 7 (7%) 9 (10%) 14 (16%) 8 (9%) 5 (6%) 1 (1%) 0 (0%)	2 (8%) 0 (0%) 0 (0%) 0 (0%) 2 (8%) 3 (12%) 0 (0%) 1 (4%)	2.27 (0.65-7.86) 4.66 (0.45-48.06) 5.90 (0.40-87.16) 9.00 (0.32-252.8) 1.21 (0.91-1.61) 0.50 (0.13-1.97) 0.93 (0.04-22.20) 0.10 (0.01-2.47)
McClung [124]	Tiludronate (91) vs placebo (48)	Gastrointestinal	31 (34%)	15 (31%)	1.09 (0.66-1.81)
Reginster [129]	Tiludronate (117) vs	Gastralgia Nausea	20 (17.1%) 11 (9.4%)	5 (16.1%) 3 (9.6%)	1.09 (0.45-2.69) 1.00 (0.30-3.38)

	placebo (32)				
Reid [72]	Alendronate (27) vs placebo (28)	Gastrointestinal Gastritis Duodenal ulcer Esophagitis	2 (7%) 0 (0%) 0 (0%) 1 (4%)	5 (18%) 1 (4%) 1 (4%) 0 (0%)	0.42 (0.09-2.00) 0.35 (0.02-8.13) 0.35 (0.02-8.13) 3.10 (0.13-73.10

Table 3.8: Summary of drug side effects reported in randomized bisphosphonate vs bisphosphonate trials

Study ID	Comparison	Side Effect	Bisphosphonate 1	Bisphosphonate 2	RR (95% CI)
Roux [132]	Tiludronate (155) vs Etidronate (79)	Gastrointestinal Abdominal pain Nausea,vomiting Fracture	32 (20.8%) 10 (6.5%) 8 (5.2%) 1 (1%)	10 (12.7%) 2 (2.5%) 2 (2.5%) 2 (3%)	1.63 (0.85-3.14) 2.55 (0.57-11.35) 2.04 (0.44-9.37) 0.25 (0.02-2.77)
Siris [76]	Alendronate (42) vs Etidronate (47)	Gastrointestinal Abdominal distention Abdominal pain Acid regurgitation Dyspepsia Melaena Nausea Leg pain Laboratory adverse experience	11 (26%) 0 (%) 3 (7%) 1 (2%) 0 (0%) 1 (2%) 2 (5%) 1 (2%) 9 (21%)	10 (21%) 1 (2%) 4 (9%) 1 (2%) 1 (2%) 0 (0%) 3 (6%) 9 (19%) 6 (13%)	1.23 (0.58-2.60) 0.37 (0.02-8.90) 0.84 (0.2-3.54) 1.12 (0.07-17.34) 0.37 (0.02-8.90) 3.35 (0.14-80.05) 0.75 (0.13-4.25) 0.12 (0.02-0.94) 1.68 (0.65-4.32)
Miller [75]	Risedronate (62) vs Etidronate (61)	Upper gastrointestinal	12 (19%)	12 (20%)	0.98 (0.48-2.02)
Barreira [119]	Olpadronate (14) vs Pamidronate (7)	Digestive	9 (64%)	7 (100%)	0.68 (0.44-1.03)

Merlotti [125]*	Zoledronate (47)* vs Pamidronate (60)	Influenza-like illness Myalgia Pyrexia Fatigue Headache Diarrhea Bone pain Pain in arm or leg Hypocalcaemia Dermatitis	4 (9%) 3 (6%) 3 (6%) 3 (6%) 4 (9%) 1 (2%) 3 (6%) 3 (6%) 3 (6%) 1 (2%)	5 (8%) 4 (7%) 4 (7%) 8 (13%) 5 (8%) 2 (3%) 6 (10%) 4 (7%) 1 (2%) 0 (0%)	1.02 (0.29-3.59) 0.96 (0.23-4.07) 0.96 (0.23-4.07) 0.48 (0.13-1.71) 1.02 (0.29-3.59) 0.64 (0.06-6.83) 0.64 (0.17-2.42) 0.96 (0.23-4.07) 3.83 (0.41-35.64) 0.42 (0.02-10.17)
Reid [130]	Zoledronate (177) vs Risedronate (172)	**Study days 1-3** Influenza-like illness Myalgia Pyrexia Fatigue Headache Rigor Nausea Bone pain **After study day 3** Pain in an arm-leg Arthralgia	 17 (9.6%) 13 (7.3%) 13 (7.3%) 12 (6.8%) 12 (6.8%) 12 (6.8%) 11 (6.2%) 9 (5.1%) 13 (7.3%) 9 (5.1%)	 7 (4.1%) 6 (3.5%) 1 (0.6%) 4 (2.3%) 7 (4.1%) 1 (0.6%) 3 (1.7%) 2 (1.2%) 12 (7%) 19 (11%)	 2.36 (1-5.55) 2.11 (0.82-5.41) 12.63(1.67.95.53) 2.92 (0.96-8.86) 1.67 (0.67-4.13) 11.66(1.53-88.72) 3.56 (1.01-12.55) 4.37 (0.96-19.95) 1.05 (0.49-2.24) 0.46 (0.21-0.99)

		Dizziness Nasopharyngitis Diarrhoea Headache Back pain Symptomatic hypocalcaemia	9 (5.1%) 9 (5.1%) 8 (4.5%) 7 (4%) 4 (2.3%) 2 (1.1%)	5 (2.9%) 14 (8.1%) 9 (5.2%) 10 (5.8%) 12 (7.0%) 1 (0.6%)	1.75 (0.6-5.11) 0.62 (0.28-1.41) 0.86 (0.34-2.19) 0.68 (0.26-1.75) 0.32 (0.11-0.98) 1.94 (0.18-21.24)
Reid [35]	Zoledronate (152) vs Risedronate (115)	Atrial fibrillation Atrial flutter Osteonecrosis jaw	1 (0.7%) 0 (0%) 0 (0%)	1 (0.9%) 2 (1.7%) 0 (0%)	0.76 (0.05-12.20) 0.15 (0.01-3.13) -
Walsh [134]	Alendronate (36) vs Pamidronate (36)	Gastrointestinal Fatigue General aches/pain Deteriorating renal function	16 (44%) 0 (0%) 4 (11%) 1 (3%)	4 (11%) 23 (64%) 16 (44%) 0 (0%)	4 (1.48-10.80) 0.02 (0.00-0.34) 0.25 (0.09-0.68) 3.00 (0.12-71.28)

*Data on the Zoledronate group were extracted from table 3 of the Merlotti [125] manuscript. In this table, the authors gathered 30 patients who took part in the first part of the study (which was included in this systematic review) plus 17 patients from the second part of the study (which was not included in this systematic review).

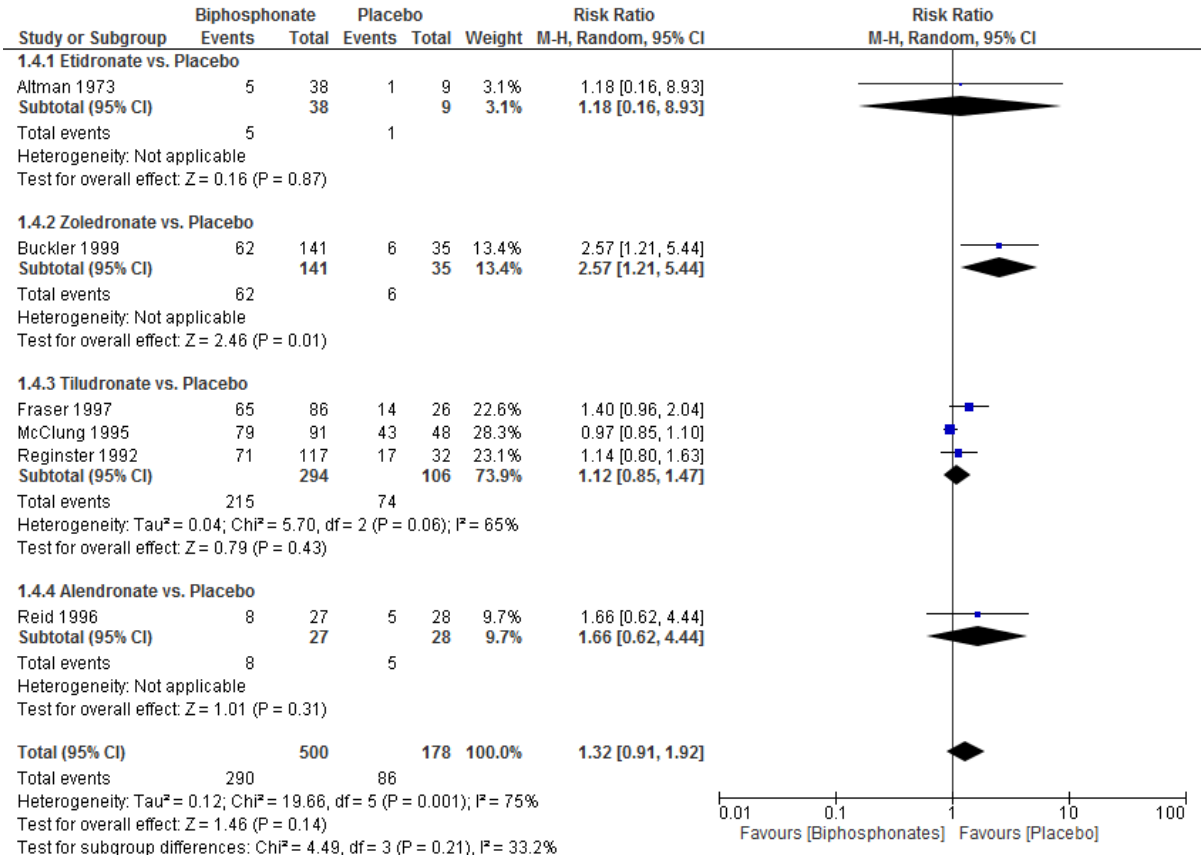
Table 3.9: Summary of drug side effects in the PRISM trial

Study ID	Comparison	Side Effect	Symptomatic	Intensive	RR (95% CI)*
Langston [36]	Intensive (661) vs Symptomatic (663)	All adverse events	3471	3429	-
		Serious adverse event	359	345	-
		Musculoskeletal	734	691	-
		Sensory	196	203	-
		Gastrointestinal	157	172	-
		Cardiovascular	327	360	-
		Arrhythmia	7 (1%)	13 (1.9%)	0.54 (0.22-1.35)
		Cancer	47	55	-
		Renal	78	98	-
		Other	1932	1850	-

Data shown are the total number of registered side effects regardless of the number of patients who had them. Only for "arrhythmia" did the authors detail the number of patients who had this side effect.

No statistically significant differences were identified when bisphosphonates vs. placebo were compared: RR 1.32 (0.91-1.92) as shown in Figure 3.9. Gastrointestinal side effects were common with oral bisphosphonates and fatigue or fever with the intravenous bisphosphonates (Table 3.7).

Figure 3.9: Number of patients who experienced side effects related to use of bisphosphonates



There were no differences within bisphosphonates such as with risedronate or alendronate to etidronate; RR 0.98 (0.72-1.35) (Figure 3.10), when newer (zoledronate, olpadronate) were compared to older (pamidronate, risedronate) aminobisphosphonates; RR 0.93 (0.73-1.19) (Figure 3.11), or when intensive with symptomatic treatment were compared; RR 1.05 (0.79-1.41). Influenza-like illness was common for the intravenous bisphosphonates. Symptomatic hypocalcaemia was uncommon (<1%) and 1 case of osteonecrosis of the jaw was recorded in PRISM-EZ. [133]

Figure 3.10: Number of patients who experienced side effects related to use of bisphosphonates (risedronate/alendronate vs etidronate)

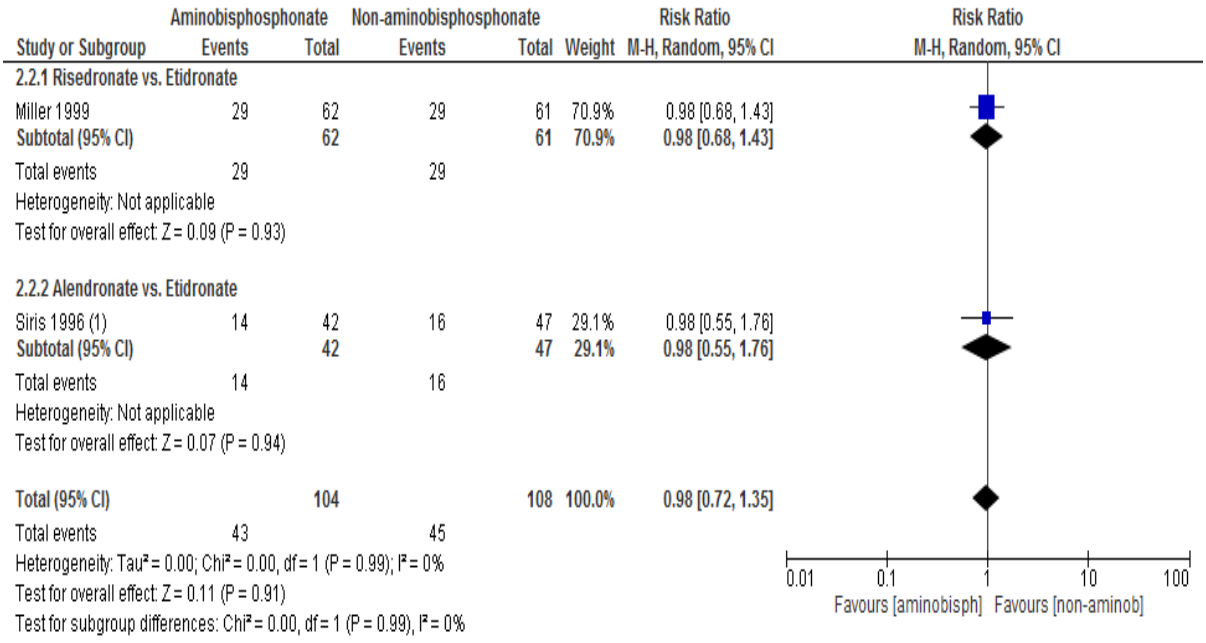
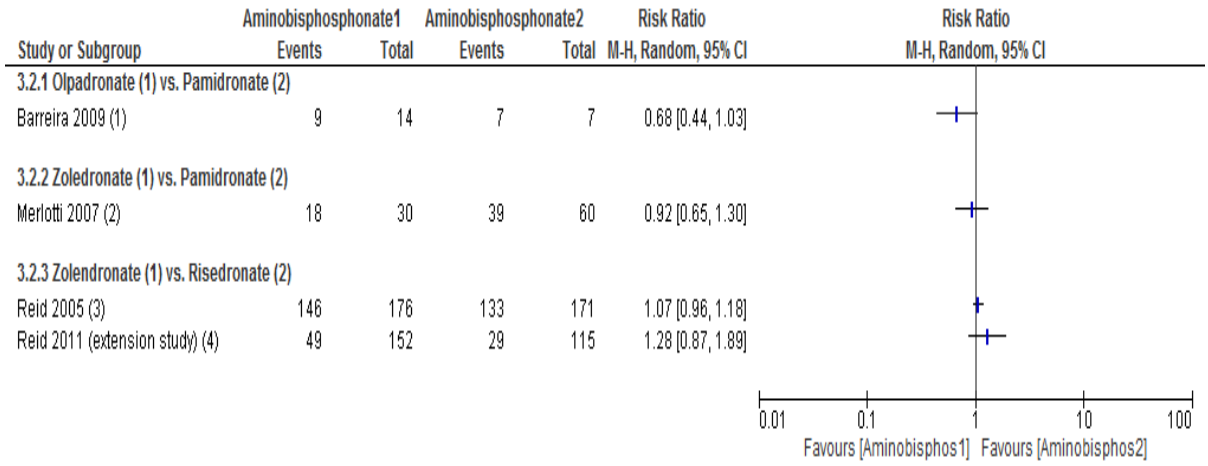


Figure 3.11: Number of patients who experienced side effects related to use of bisphosphonates (newer vs older bisphosphonates)



Footnotes

(1) All patients with pamidronate reported at least one digestive event.

(2) Adverse events: influenza-like illnes, myalgia, pyrexia, fatigue, headache, diarrhea, bone pain, pain in arm or leg, hipocalcemia and dermatitis.

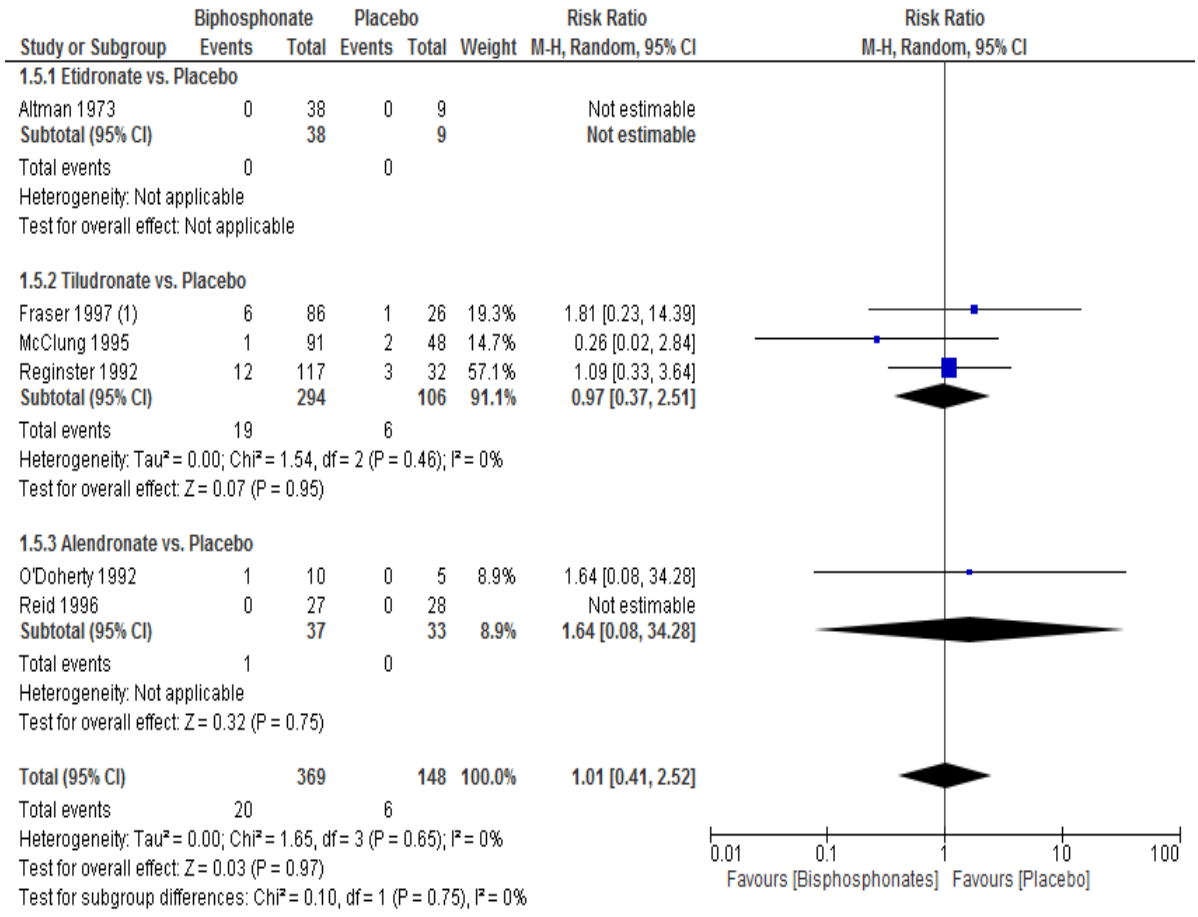
(3) Serious adverse event (9/176 vs. 11/171): chest pain, infection, fracture (femur, humerus, spinal), back pain, acva, endometrial hyperplasia, asthma, dyspnoea, cellulitis orbital,...

(4) Serious adverse events

3.4.13.7 Withdrawals due to Side Effects

Discontinuations due to side effects were available and analysed for 13 trials. The pooled estimate for the comparison between bisphosphonates and placebo [72, 117, 123, 124, 126, 129] demonstrated no statistical difference for the risk of discontinuing medication due to side effects [RR 1.01 (0.41-2.52)] in Figure 3.12. Results were consistent across trials, with a low rate of withdrawals in both treatment groups.

Figure 3.12: Comparison of the numbers of patients receiving either bisphosphonates or placebo who withdrew due to adverse events



There were no differences within bisphosphonates: 1) between two non-aminobiphosphonates [132]; RR 2.55 (0.57-11.35) (Table 3.5) 2) between aminobisphosphonates and non-aminobisphosphonates [75, 76]; RR 0.69 (0.25-1.89) (Figure 3.13), 3) between two aminobisphosphonates [125, 130, 134]; RR 0.93 (0.37-2.35) (Figure 3.14), or 4) between intensive and symptomatic treatment [36] RR 1.05 (0.79-1.41)

Figure 3.13: Comparison of the numbers of patients receiving aminobisphosphonates and non-aminobisphosphonates who withdrew due to adverse events

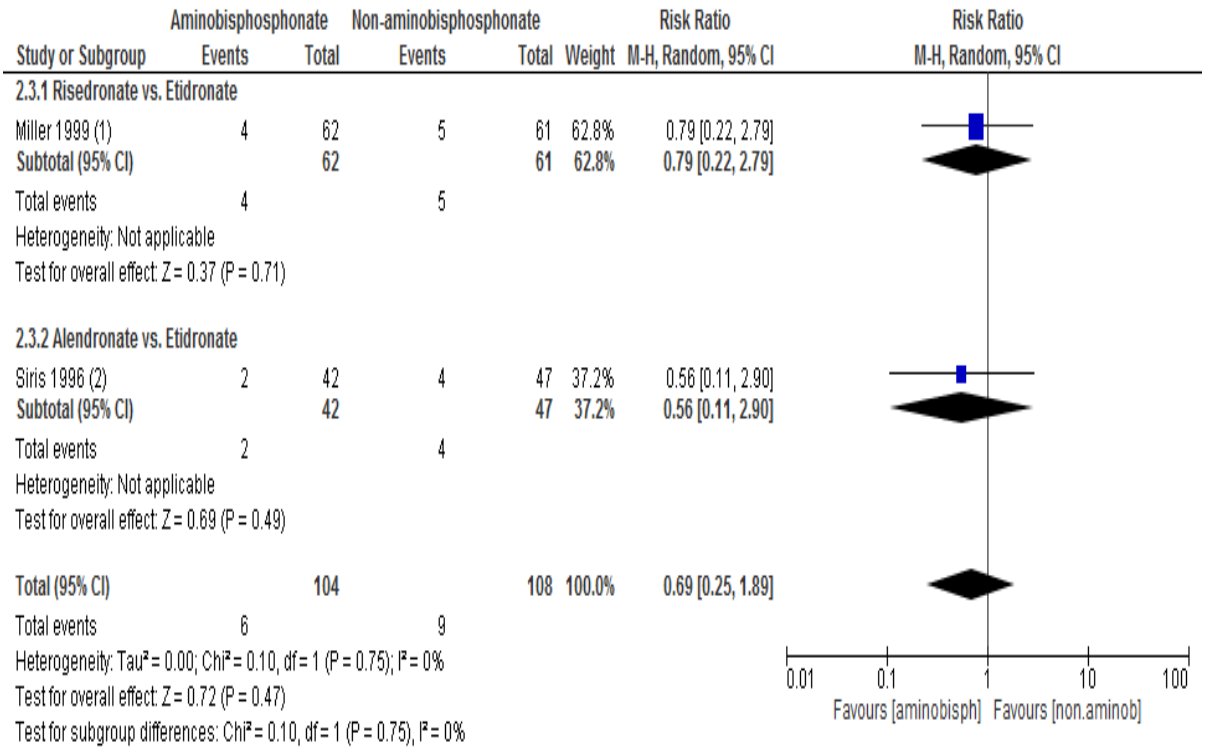
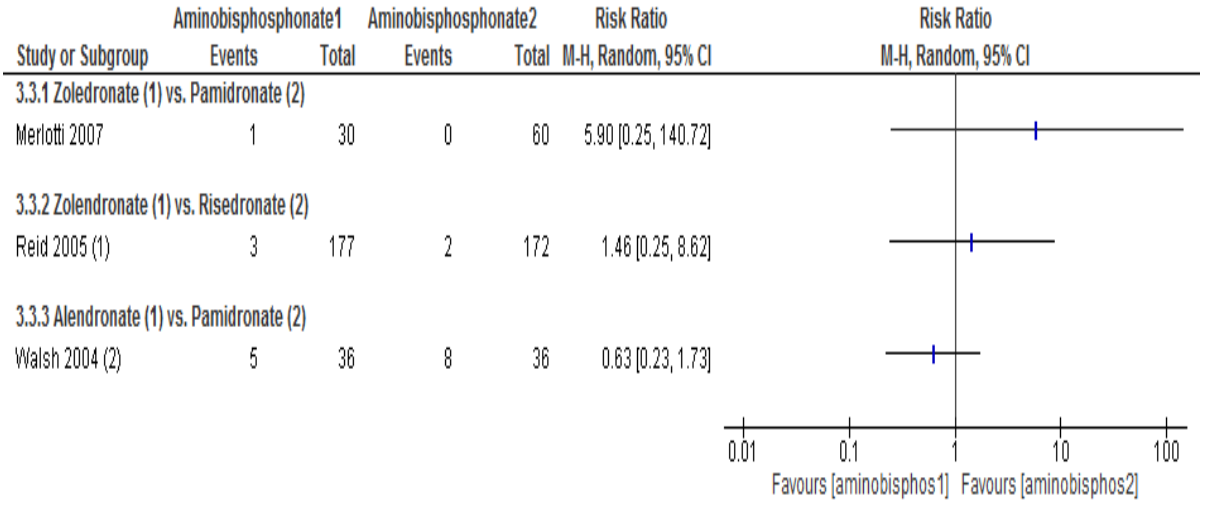


Figure 3.14: Comparison of the numbers of patients receiving different aminobisphosphonates who withdrew due to adverse events



3.4.14 Minor outcomes

3.4.14.1 Relapses due to Recurrence of Bone Pain.

Relapses due to recurrence of bone pain were analysed in only one study. [123] When compared to placebo, tiludronate achieved a significant reduction in the number of patients who relapse due to bone pain [RR 0.51 (0.32-0.80)].

3.4.14.2 Effect on Serum Total ALP Activity.

Changes in serum bone markers, especially changes in serum total ALP activity were considered as the primary outcome in all but one trial [36] and its extension. [133] Biphosphonates achieved a significantly higher reduction in serum total ALP activity when compared to placebo: with a mean difference in the reduction in ALP activity of 50.09% (32.46-67.72) (Figure 3.15). In line with the previous outcome, a high proportion of patients normalised their ALP levels: RR 9.96 (3.74-26.58) (Figure 3.16).

Figure 3.15: Mean percentage change from baseline in serum total ALP level

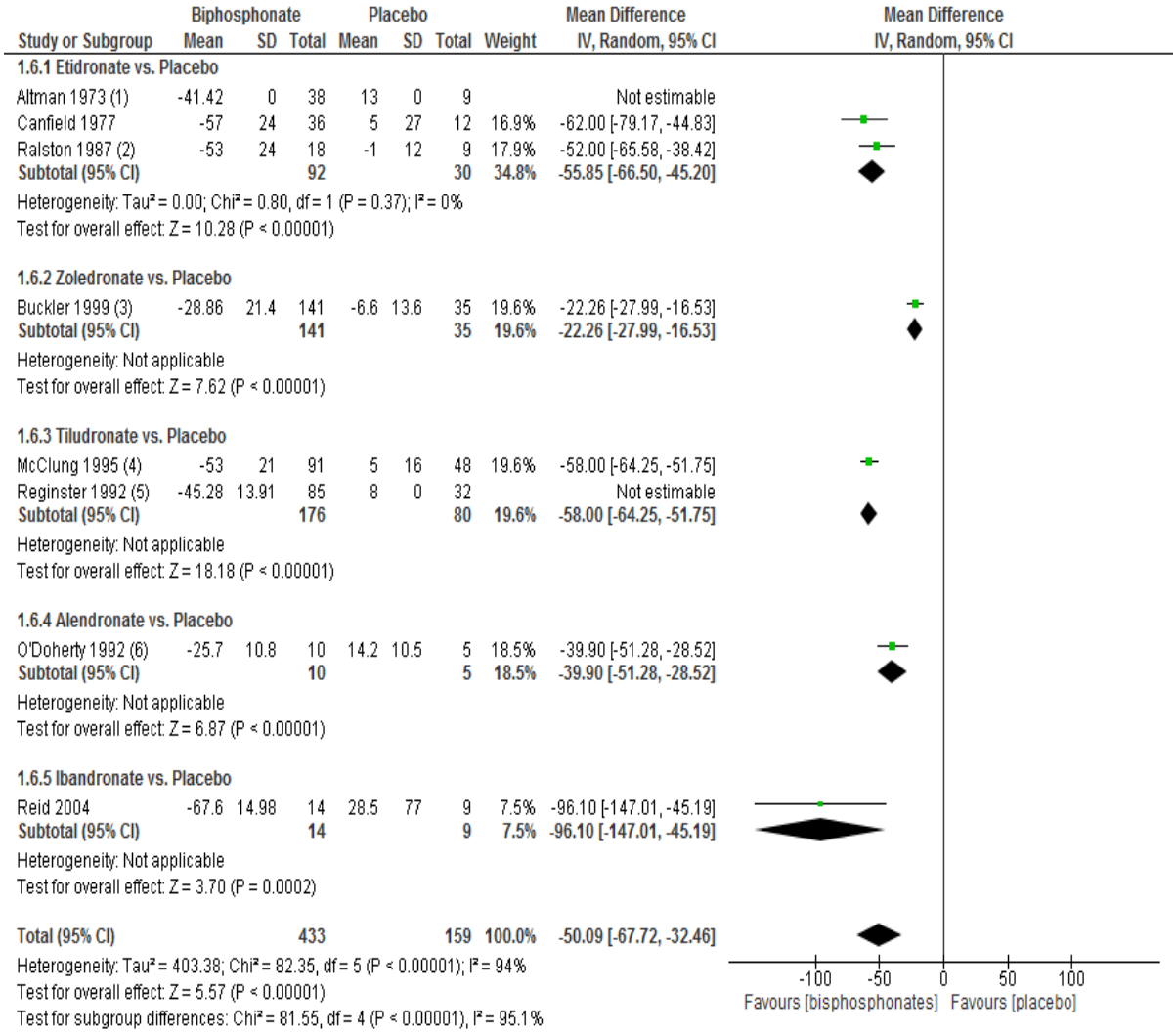
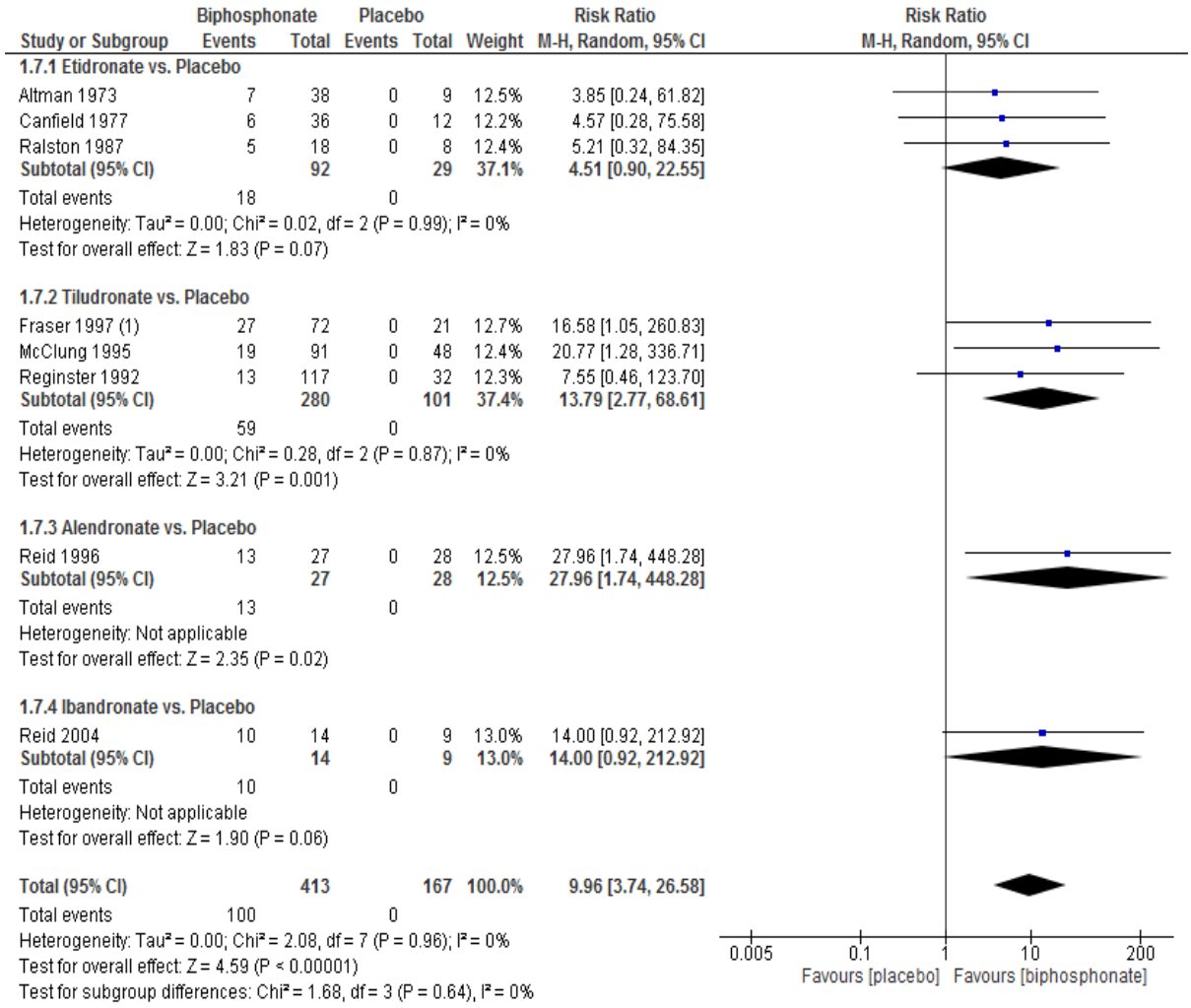


Figure 3.16: Number of patients who normalized ALP level



Within non-aminobisphosphonates, tiludronate was more efficacious than etidronate [132], with a RR 2.27 (1.16-4.43) for ALP normalisation (Table 3.5)

The aminobisphosphonates had a higher effect on serum bone markers than the non-aminobisphosphonates as shown in the comparisons between risedronate [75] or alendronate [76] versus etidronate: with a mean difference in the reduction in ALP activity of 40.95% (32.81-49.09) (Figure 3.17), and RR 4.30 (2.72-6.79), NNT 2 (1-4) for ALP normalisation (Figure 3.18).

Figure 3.17: Mean percentage change from baseline in serum total ALP between risedronate or alendronate versus etidronate

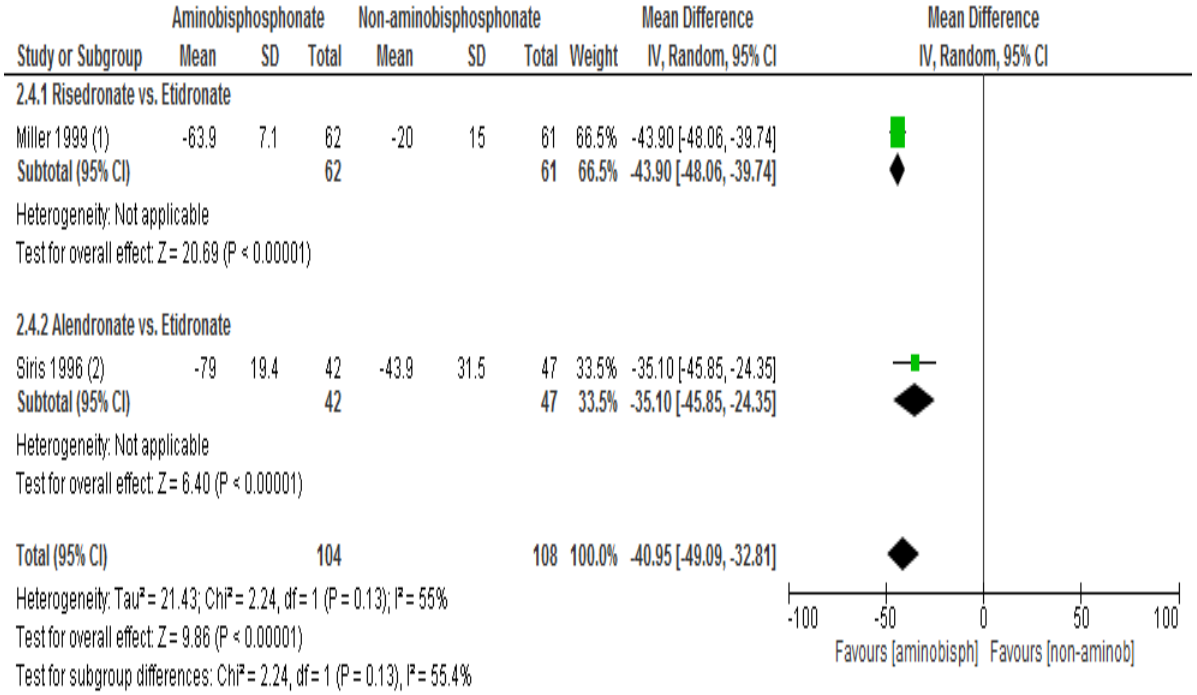
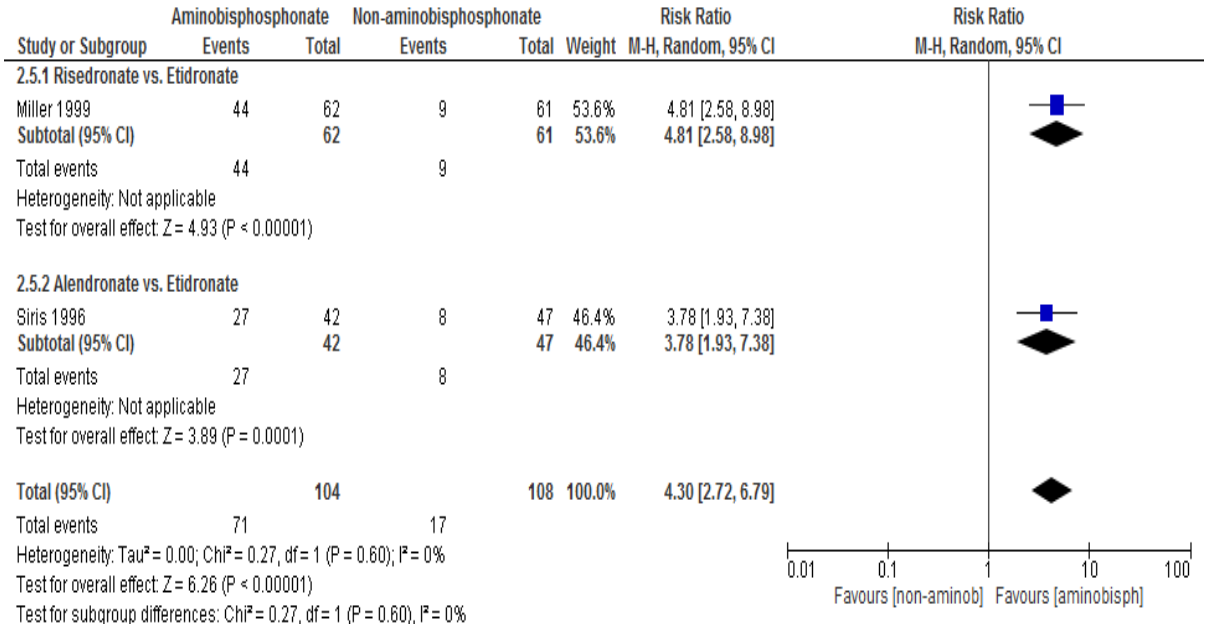


Figure 3.18: Number of patients who normalised ALP when treated with risedronate or alendronate versus etidronate



Within aminobisphosphonates, zoledronate was the more efficacious. The mean difference in the reduction in ALP activity for zoledronate when compared with risedronate was 22.7% (19.27-26.13) (Figure 3.19), and RR 1.53 (1.33-1.76), NNT 2 (1-12) for ALP normalisation (Analysis 3.5). In addition, alendronate was more efficacious than pamidronate [134] RR 1.48 (1.09-2.00) for ALP normalisation (Figure 3.20).

There were differences when intensive treatment was compared to symptomatic treatment [36], as much in the mean reduction in ALP activity 22.5% (15.4-29.6), as in the percentage of patients who normalised the ALP level [RR 1.26 (1.18-1.36)].

Lastly, when etidronate was compared with etidronate plus calcitonin, the combination showed a higher reduction in ALP than etidronate alone: 71% at 6 months vs. 56% (no confidence interval was shown in manuscript). [127]

Figure 3.19: Mean percentage change from baseline in serum total ALP in patients receiving different aminobisphosphonates

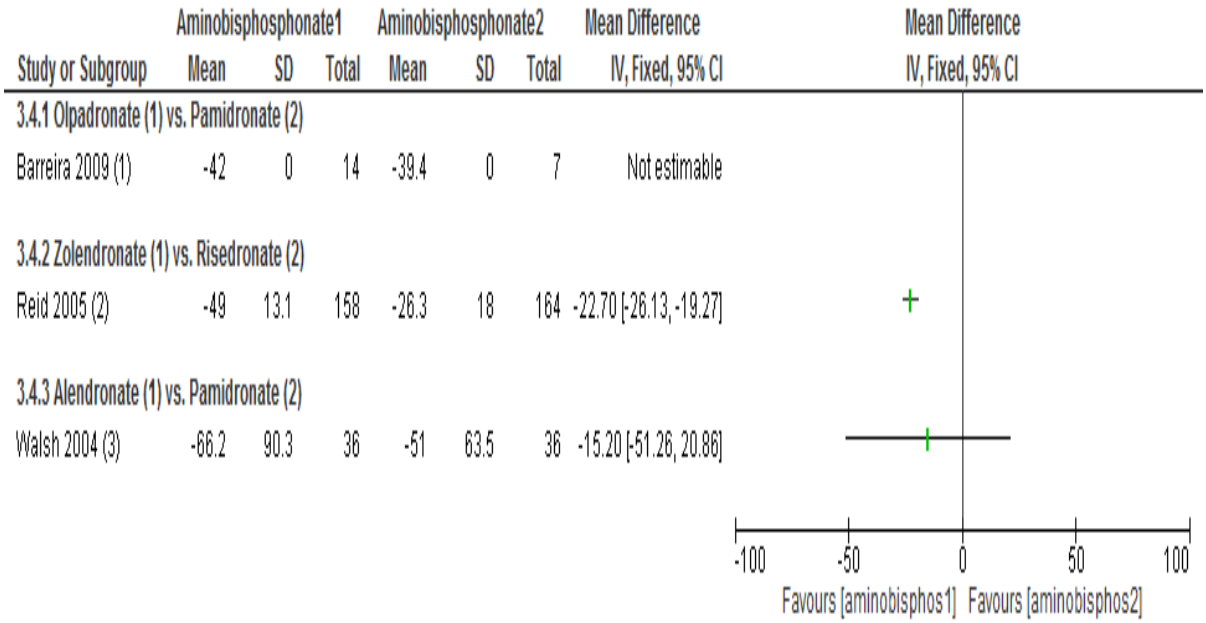
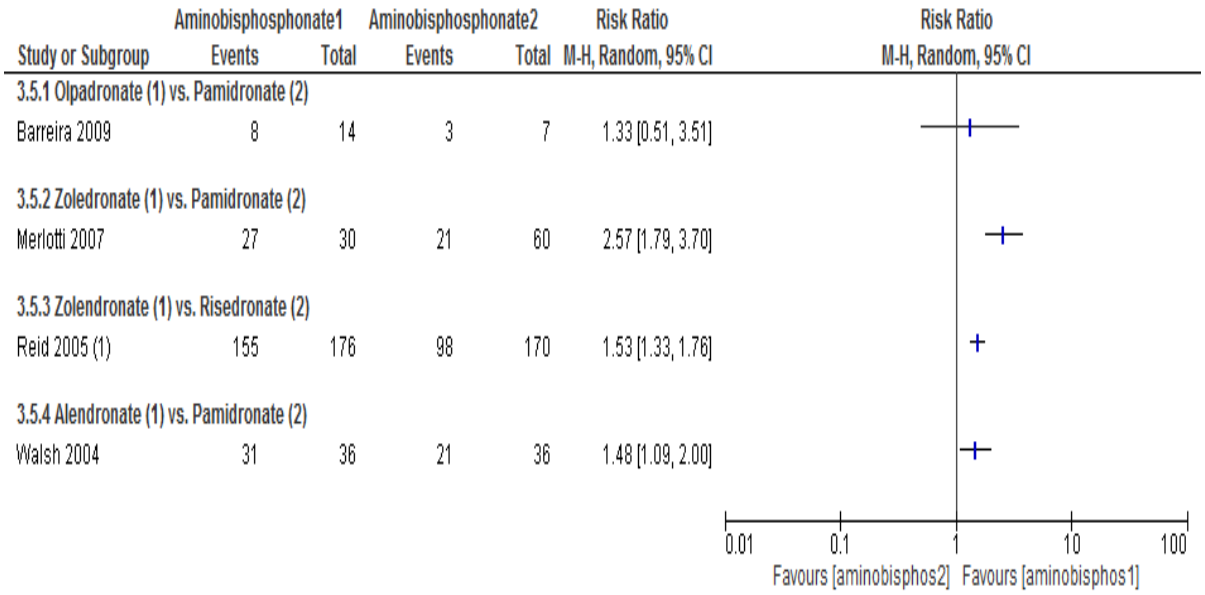


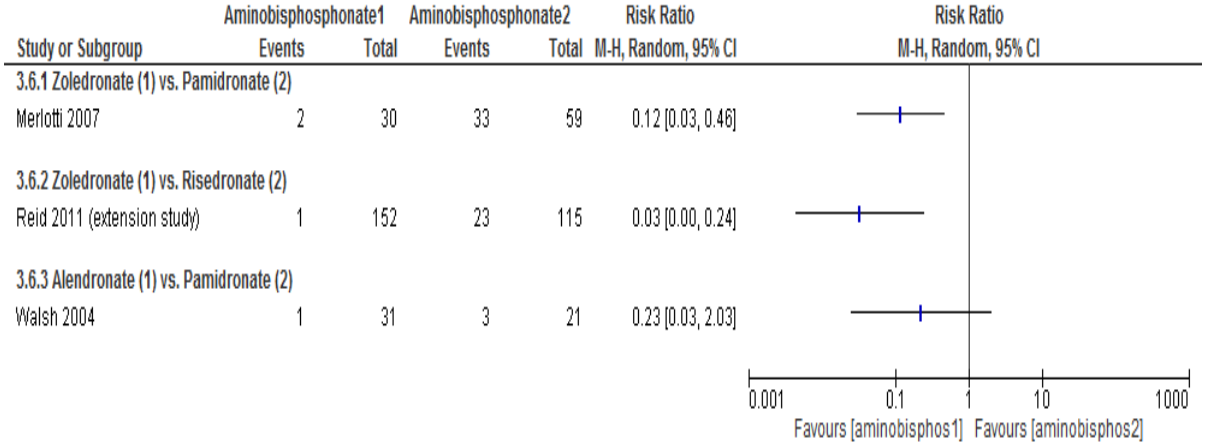
Figure 3.20: Numbers of patients who normalised ALP when treated with different aminobisphosphonates



3.4.14.3 Relapses due to Recurrence of Increased Serum ALP Level.

Three trials address relapse due to recurrence of increased serum ALP level. Between aminobisphosphonates and non-aminobisphosphonates, risedronate was more efficacious than etidronate [RR 0.25 (0.05-1.11)]. [75] Within aminobisphosphonates, zoledronate was more efficacious when compared to pamidronate [125] or risedronate [130]; RR 0.06 (0.01-0.42), NNT 3 (3-5) (Figure 3.21).

Figure 3.21: Number of patients who had biochemical relapse with increased ALP receiving different aminobisphosphonates



3.5 Discussion

3.5.1 Summary of Main Results

Evidence from seven studies in 481 people contributing data to the primary outcome of this review showed that bisphosphonates are effective in relieving bone pain. There was no evidence that bisphosphonate therapy prevented fractures but few studies were designed to study the effects of treatment on the occurrence of fractures. There was limited evidence to draw firm conclusions about the impact of bisphosphonates on hearing thresholds, deafness, bone deformity, fractures or the need of orthopaedic surgery. When zoledronate was compared with risedronate, a marginal improvement in some aspects of quality of life occurred. . Differences were also observed in quality of life with long-term follow up but this was restricted to the subgroup of patients that had normal levels of ALP after the core study. [35]

The results from the present study show that bisphosphonates were highly efficacious at reducing biochemical markers of bone turnover. Aminobisphosphonates were more efficacious than non-aminobisphosphonates, and

amongst aminobisphosphonates, zoledronate was the most efficacious.

Low quality evidence was identified for a lack of harm associated with bisphosphonate treatment. Minor gastrointestinal side effects were common with trials for oral bisphosphonates, whereas a transient influenza-like illness or pyrexia (three days or less) was commoner with the intravenous bisphosphonates. Serious side effects were rare, and the rate of withdrawals because of side effects was low. There were no clinically significant differences in side effects when different bisphosphonates were compared.

The PRISM trial which involved 1331 participants [36] addressed the issue of a "treat to target" design using bisphosphonates in patients with PDB with fractures as the primary endpoint. The trial compared two strategies. In the symptomatic group, analgesia and bisphosphonates (if no response to analgesia) were given with the aim of treating bone pain. In the intensive group bisphosphonates were given with the aim of normalising ALP levels. This study showed no differences in fractures between the treatment groups or in secondary outcomes, including pain relief, hearing thresholds, orthopaedic surgery or quality of life. An extension of this study which involved 502 participants [133] showed no benefit of intensive treatment on quality of life and there was a non-significant trend for an increased risk of fractures and orthopaedic procedures in the intensive treatment group.

3.5.2 Overall Completeness and Applicability of Evidence

The results in the present study were derived from trials identified through an extensive and systematic literature search, including articles in all languages. Trial registers were searched to find potentially relevant studies which had yet to be published.

The included trials covered the usual spectrum of elderly patients diagnosed as PDB. However, not a single study included patients without raised serum bone markers. While the inclusion of these trials allowed us to cover a wide range of patients, these results should not be applied to patients who have neither bone pain nor serum

bone marker abnormalities. It is uncertain whether bisphosphonates could have an effect over misshapen bones in these subjects, in order to avoid long-term complications such as bone fractures, the need for orthopaedic surgery or progression of deafness in patients with skull involvement.

Most of the studies planned for the change in serum bone turnover markers as the primary outcome. While the treatment group always achieved a reduction of serum bone turnover markers compared to the control group, it was not possible to know if this biochemical effect translated into clinical benefits for patients as most of the trials did not address long-term patient-oriented outcomes. Only pain relief, as a short-term patient-oriented outcome, was addressed in most of the trials.

Based on the available data, there is no clinical benefit in adopting a strategy of treating with bisphosphonates with the aim of normalising ALP in PDB. A long-term study of intensive bisphosphonate treatment showed no benefit in quality of life as compared with symptomatic treatment and showed a trend towards an increased risk of fractures with intensive treatment, although the difference between groups was not significant.

3.5.3 Quality of the Evidence

The 'summary of findings' table only provides a comparison between bisphosphonates and placebo. For the seven patient-important outcomes described, evidence ranged from very low to moderate in four outcomes; and the effect was uncertain, (because of the lack of trials addressing the outcome) in the remaining three outcomes.

The quality of the evidence for bone pain relief was moderate. It was downgraded by one level, due to a high risk for attrition bias in three of the studies and a high risk for reporting bias in another three studies. None of the included studies for the comparison of bisphosphonates against placebo had a high risk for performance bias. Despite the number of high-risk studies, the evidence was not downgraded by 2 levels, as the outcome did not change in the sensitivity analysis excluding high risk

studies.

The quality of the evidence for fracture prevention was low. It was downgraded by three levels as most of the information was from studies at risk of bias (two studies with high risk for attrition bias and one study with high risk for reporting bias). The design of most studies were not suitable to examine the long-term impact on fractures as the mean follow-up period was six months, and there were a low number of events, resulting in a wide CI.

The quality of the evidence for side effects was low. It was downgraded by one level because two of the studies had high risk for attrition bias. It was further downgraded by another level because of inconsistency. The kind of side effects considered was heterogeneous within studies. In addition, considerable heterogeneity was shown on meta-analysis. However, only one study showed more adverse events in the placebo group than in the bisphosphonate group. A sensitivity analysis without this study had no heterogeneity.

The quality of the evidence for withdrawals due to side effects was moderate. It was downgraded by one level because half of the studies were at high risk of bias (High risk for attrition bias in three [117, 126, 129] and high risk for reporting bias in one [126]). Although there was a wide CI because of the low number of events, this outcome was not downgraded as the relative risk was close to one.

Only a few trials with comparisons between bisphosphonates were identified. The quality of evidence for comparisons between two non-aminobisphophonates was low, as only one trial compared tiludronate vs. etidronate. The quality of evidence for the comparison between amino and non-aminobisphosphonates was low as there were only two small trials. Lastly, evidence for the comparison within aminobisphosphonates was also low as only four trials were included. In addition two of them were open label, and one was published only in abstract form. The quality of the evidence for the comparison between zoledronate and risedronate is drawn from a bigger trial, with a low risk of bias for most of the endpoints assessed.

The evidence drawn from the PRISM trial, and it's extension study which compared

two treatment strategies, was limited by a high risk of bias for patient reported outcomes due to its open-label design. However the PRISM and PRISM-EZ studies were the only trials which collected data on fractures and orthopaedic procedures.

3.5.4 Potential Biases in the Review Process

The principal limitation of the review was the scarce evidence found in the published literature and its low quality for the patient-orientated outcomes of main interest such as fractures and progression to deafness. Many of the trials included were assessed as having a high risk of bias or were relatively small and underpowered.

For the major outcome of change in bone pain, the heterogeneity of pain definitions and the lack of any generally standardized way to assess bone pain made the comparisons between studies difficult. In addition, differentiation of the cause of the pain was difficult as pain could be related to increased metabolic activity in pagetic bone, coexisting arthritis, nerve compression because of misshapen bones or other causes.

A potential source of heterogeneity was the lack of uniform definitions of adverse events reported in the RCTs described in this review. Adverse effects were not assessed as a primary outcome in any of the trials, and in many studies were not assessed at all. Therefore, reporting of these outcomes was frequently incomplete and the studies were not sufficiently powered to address rare adverse effects. An attempt to avoid any outcome-reporting bias was made by asking authors for additional data on adverse events. However, since the studies included in this review were carried out many years ago, many author requests remained unanswered or the study authors replied that it would not be feasible for them to access the original data of the trials. Another limitation of evaluating data on side effects from a summary meta-analysis is that participants in RCTs tend to be healthier, with less co morbid disease, and therefore the results may not reflect daily clinical practice. In addition, in this review, five trials [72, 76, 123, 130, 132] excluded

patients with pre-existing gastrointestinal diseases.

Another methodological limitation concerns the approach used for concealment of treatment allocation, which was not reported for most trials. Five of the 20 trials concealed allocation, and for the remainder it was unclear.

An additional limitation was the length of follow-up in the trials. Most of the studies were short, with a duration of six months or less. It is difficult to extrapolate beyond the duration of follow-up of studies in this review with respect to the long-term impact on fractures and other complications of PDB.

3.5.5 Agreements and Disagreements with Other Studies or Reviews.

In this systematic review the evidence from all randomised controlled trials that were designed to test bisphosphonates as a treatment for Paget's disease of bone has been summarised. No other systematic review has been conducted on the effects of bisphosphonates in Paget's disease of bone, but there were four guidelines available: the Bone and Tooth Society of Great Britain and the National Association for the Relief of Paget's Disease guideline [3], the Japanese guideline [135], the Belgian guideline [136] and the Endocrine Society guideline. [40]

This present review is in agreement with British guidelines [3], which state "bone pain is the only complication of Paget's disease of bone for which there is firm evidence that specific anti pagetic therapy is associated with clinical benefit". Four of the five references used for this statement are included in the present review. [72, 117, 128, 129] The authors also stated that there is no evidence to support the use of specific treatment to prevent deafness, fractures, osteoarthritis, progression to bone deformity or spinal cord compression. Additionally the Japanese and Belgian guidelines support pain as the only evidence-based indication for the treatment of PDB. The most recent review [41] highlights the inclusion of the zoledronate vs. risedronate trials [130] that showed a better profile for zoledronate for normalising alkaline phosphatase and evidence for benefit in some aspects of quality of life. The present review disagrees with certain aspects of the Endocrine Society guideline,

which suggests that bisphosphonate therapy should be given to normalise biochemical markers of bone turnover with the aim of preventing complications. [40] No evidence of benefit for this strategy was found and there was some evidence that it may be harmful. [133]

3.6 Conclusions

3.6.1 Implications for Practice

Based on the studies in this review, there is moderate quality evidence that bisphosphonates improve pain in PDB. There is insufficient evidence to determine the effects of bisphosphonates over other complications and their impact on QoL. There is limited evidence on the effects of long-term treatment on complications such as fractures, deformity, progression of deafness or the need for orthopaedic surgery. Within bisphosphonates, there is low quality evidence that zoledronate may have a better balance between benefit and harms for the treatment of Paget's disease of bone when compared with risedronate or pamidronate. No increased incidence of adverse effect was detected, but concerns exist regarding the low quality of the evidence and the unsuitable design of most of the trials to detect rare side effects. Lastly, based on this present review, there is no evidence of benefit for a treat-to-target strategy aimed at normalising biochemical markers of bone turnover, with some evidence to suggest that this may be harmful.

3.6.2 Implications for Research

The existing data has not resolved the question of whether bisphosphonates can prevent long-term outcomes such as fractures, deafness progression or the need of orthopaedic surgery. Appropriately designed clinical trials including long-term evaluations and larger sample sizes are needed. Additional research is needed to clarify the impact of bisphosphonates in QoL of patients with PDB, as the evidence

show that these drugs have a limited impact on QoL. The role of bisphosphonates in asymptomatic patients with biochemical markers of bone turnover within normal range also merits further investigation. Finally, there are no data to suggest that maintaining ALP levels within the normal range reduces the risk of complications

Chapter 4

Long term effects of Intensive and Symptomatic Management on clinical outcomes in PDB

Abstract

This study (PRISM-EZ) which was an extension of a pragmatic randomised controlled trial involving patients with PDB recruited from 39 secondary care referral centres in the UK was designed to compare the effects of intensive bisphosphonate therapy aimed at suppressing bone turnover with standard care in which bisphosphonates were only given for symptom control on clinical outcome in PDB. Of the 502 participants enrolled, 270 continued with intensive treatment and 232 with standard care. Bisphosphonates were routinely prescribed in the intensive group with the aim of suppressing bone turnover using zoledronate as the treatment of first choice. Participants in the standard care group received bisphosphonates and other treatments only if bone pain was present. The primary outcome was fracture. Secondary outcomes were ALP concentrations, orthopaedic surgical procedures; quality of life assessed by the SF36 questionnaire, bone pain and adverse events. Serum ALP concentrations were lower in the intensive group at baseline and throughout the study. Changes in the SF36 physical component summary, arthritis specific health index and bodily pain at 1 year favoured intensive therapy but at three years changes in the mental component summary favoured symptomatic therapy. All differences were below the threshold that is considered clinically significant. Fractures were more common hazard ratio [95% confidence interval], 1.90 [0.91 to 3.98] and orthopaedic surgery was required more frequently 1.53 [0.63 to 3.72] in the intensive group. Although statistical significance (in support of a higher rate of events in the intensive arm) was obtained in PRISM-EZ when both these outcomes were combined, it is acknowledged that this composite outcome was not a pre-specified outcome measure, that combining entirely different outcome measures is not conventional and that the total numbers of events used to generate this finding was low. Irrespective of treatment group, fractures were more common in patients that had received bisphosphonates during the extension (14.1% vs.1.5%,

p<0.0001). Serious adverse events, which included one case of osteonecrosis of the jaw, were more common with intensive therapy (32.2% vs. 28.8%, relative risk 1.28 [RR of 0.96 to 1.72]. In summary, long term intensive bisphosphonate therapy confers no clinically important benefit over standard care in PDB and is associated with a non-significant increased risk of fractures, orthopaedic procedures and serious adverse events. Bisphosphonate therapy in PDB should be used for the treatment of symptoms rather than trying to suppress ALP concentrations

4.1 Introduction

PDB is a common skeletal disorder with a strong genetic component that affects up to 2% of Caucasians over the age of 55 years. [41] It is characterised by increased bone resorption, coupled to increased and disorganised bone formation at one or more skeletal sites. Many patients with PDB never come to medical attention [25], but bone deformity, pathological fracture, deafness and secondary osteoarthritis and bone pain are common in those that do present clinically, significantly impairing quality of life. [25, 71, 137] Bisphosphonates are highly effective at suppressing the elevated bone turnover that is characteristic of PDB [75, 76] and are an effective treatment for bone pain associated with PDB. [3, 55] It has previously been suggested that normalisation of bone turnover with bisphosphonates might also be of benefit in preventing complications of PDB. [31, 138] Recent clinical guidelines have advised that potent bisphosphonates should be administered to most patients with PDB with the aim of reducing biochemical markers of bone turnover to within the lower half of the normal range. [40] At the present time however there is no evidence that this strategy is effective in preventing complications. [139] The PRISM study was initiated in 2001 with the aim of determining whether long-term suppression of bone turnover with intensive bisphosphonate therapy conferred any clinical benefit over symptomatic treatment inpatients with PDB. [36] The results of

the core study showed that intensive and symptomatic treatment strategies yielded similar results with regard to occurrence of fractures, requirement for orthopaedic surgery, hearing loss, bone pain, quality of life and adverse events. [36] Here, the results of a three-year extension of the PRISM trial (PRISM, extension with zoledronate; PRISM-EZ) in which the same treatment strategies were continued but where the highly potent bisphosphonate zoledronate was used as the treatment of first choice in the intensive arm, are reported.

This work undertaken in this study was performed by the author (AT), Prof Stuart Ralston (SHR), Dr. Kirsteen Goodman (KG), Allan Walker (AW), Jemma Hudson (JH), Graeme S MacLennan (GSM), Prof. Peter L Selby (PLS), Prof. William D Fraser (WDF) and members of the PRISM-EZ Trial Group. Author contributions are as follows:

Study conception and design: SHR
Acquisition of data: AT, SHR, KG, AW, PLS
Analysis and interpretation of data: AT, JH, GSM, SHR, AW, WDF, PLS
Drafting of manuscript: AT, SHR
Critical revision of the manuscript for important intellectual content: AT, SHR, KG, GSM, PLS, WDF, AW
Statistical analysis: JH, GSM
Obtaining funding: SHR, PLS, WDF
Study supervision: KG, SHR, AW

4.2 Methods

4.2.1 Study Design

The design of the PRISM study has previously been reported. [36] In brief, the treatment goal in the intensive arm was to suppress bone turnover by reducing and

maintaining serum total alkaline phosphatase (ALP) concentrations within the reference range whereas the treatment goal in the symptomatic arm was to treat bone pain thought to be due to PDB with analgesics or with bisphosphonates if the response to analgesics was inadequate. Participants who completed the PRISM study were invited to take part in a three-year extension (PRISM-extension with zoledronate; PRISM-EZ) in which the same treatment strategies were employed but where the highly potent bisphosphonate zoledronate was used as the bisphosphonate of first choice in the intensive arm. Enrolment into the study commenced in January 2007 and the study ended in January 2012.

4.2.2 Randomisation and Study Treatment

Patients were randomised into one of the two treatment groups on entry to PRISM using a minimisation algorithm to ensure balance for key prognostic variables.[36] Minimisation criteria were ALP values at baseline (within normal range, elevated up to twice the upper limit of normal, or elevated more than twice the upper limit of normal), previous bisphosphonate treatment (yes/no), presence of the disease in a weight-bearing limb (yes/no), bone deformity (yes/no), skull involvement (yes/no) and bone pain (yes/no). [36] During PRISM-EZ participants were continued in the same treatment group as they had been allocated in PRISM. In the symptomatic group clinicians were instructed to give no treatment for PDB unless the patient had bone pain which was thought to be caused by increased metabolic activity of PDB. These patients were initially treated with analgesics or non-steroidal anti-inflammatory drugs (NSAID) and those that failed to respond adequately were treated with bisphosphonates. The treatment goal in the intensive arm was to suppress bone turnover with bisphosphonate therapy with the aim of maintaining serum total ALP concentrations within the normal range irrespective of symptoms. Zoledronate was the treatment of first choice within the intensive arm.

4.2.3 Outcome Measures

Participants were reviewed on an annual basis and details were collected on treatments received for PDB and other relevant variables. The primary outcome was clinical fracture. Other secondary outcomes included orthopaedic procedures, serum total ALP concentrations; bone pain and health related quality of life. Quality of life was measured using various tools including the Medical Outcomes Study 36 Item Short-Form Health Survey (SF-36) questionnaire [140]; the Stanford Health Assessment Questionnaire Disability Index [141] (HAQ); the EuroQoL questionnaire, (EQ-5D); and the arthritis specific version of SF36 (ASHI). [142] Bone pain was recorded as being present at entry to PRISM-EZ and at each visit, physicians were asked to assess whether they considered that the bone pain was attributable to PDB. The commonest criteria used by physicians for attributing bone pain to PDB were; localisation of pain to an affected site; response of pain at that site to previous treatment with bisphosphonate; pain at rest and pain at night. [36] Within the PRISM-EZ study collection of quality of life was optional depending on the resources available at study sites. Data on quality of life were available on 388/503 (77%) of subjects on PRISM-EZ. Fractures and orthopaedic procedures were validated against medical records and x-ray reports at participating centres by assessors blinded to treatment allocation. Serum total ALP was measured according to standard techniques by the biochemistry laboratories at participating centres. The measured ALP values were normalised to the upper limit of the local laboratories' reference range to give adjusted ALP values so that results could be compared across centres. The adjusted values were categorised into four groups; low normal (ALP below the 50th centile of the local reference range); normal (between the 50th - 100th centile of the reference range); high (up to three times above the upper limit of the reference range) and very high (more than three times above the upper limit of the reference range).

4.2.4 Statistical Analysis

A power calculation was not performed since this was an extension of an existing study. The statistics are reported as number and percentages or numbers and mean ± standard deviation (SD) as appropriate unless otherwise stated. Since participants in PRISM-EZ opted in to long-term follow-up baseline characteristics between groups were compared using standardised differences, values of greater than 0.1 indicating imbalance. [143] Inverse probability of treatment weighting (IPTW) was used to adjust analyses for any potential imbalance between groups. [143] In IPTW, a weight is calculated for each subject that is equal to the inverse of the probability of receiving the treatment that was actually received. [144] These weights are incorporated into the analyses to minimise the effects of observed confounding. [144]

In the current study, the weights were propensity scored using logistic regression with treatment as the independent variable. [143] The covariates that were included are those described in Table 4.1. Flexible parametric models were used for the time-to-event outcomes of fracture and orthopaedic procedures. [145] Estimates of the effect sizes are presented as hazard ratios with 95% confidence intervals. The quality of life data and ALP measurements were analysed using linear mixed models with a random effect for participant and centre to reflect the repeated measures nature of the data. All available data at each follow-up time-point was used and no adjustment was made for missing data. [146] All statistical analyses were IPTW adjusted unless otherwise stated.

4.2.5 Ethics

All participants gave written informed consent to be included in the study. The trial was approved by the UK Multicentre Research Ethics Committee for Scotland (MREC01/0/53); by local ethical review boards in the participating study centres and by the Medicines & Healthcare Products Regulatory Authority (CTA 21583/0002/001-

0001). The study was included in the controlled clinical trials register (www.controlled-trials.com) and assigned the reference number ISRCTN12989577.

4.2.6 Patient Involvement

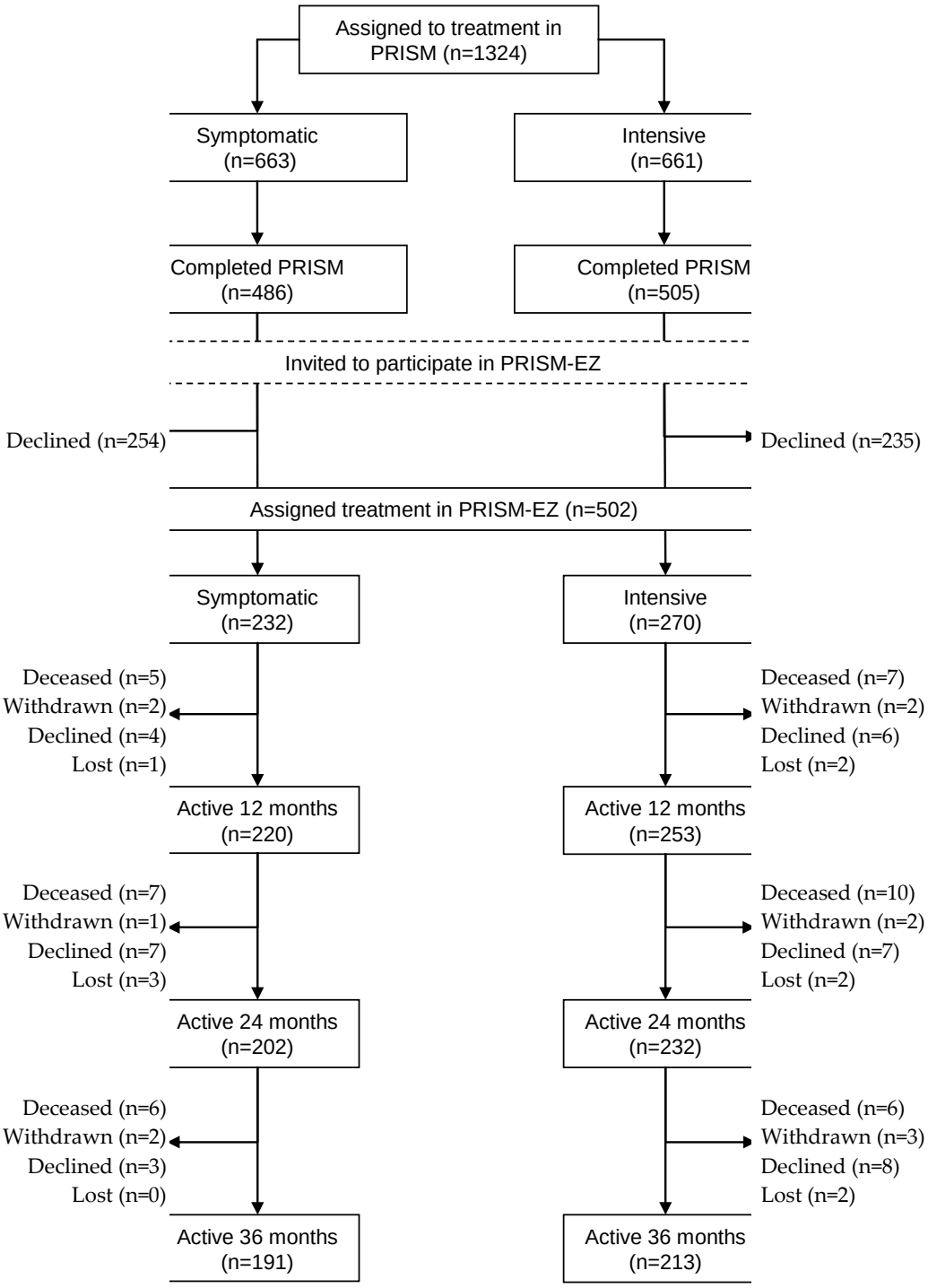
The research questions in the PRISM study were developed in consultation with patient representatives from the Paget's Association – a UK based patient support organisation and a representative from the Paget's Association served as a member of the trial steering committee on both PRISM and PRISM-EZ.

4.3 **Results**

4.3.1 Characteristics of the Study Population

The disposition of subjects is shown in figure 4.1. 991 patients who completed the PRISM study were invited to take part in the extension study and 502 (50.7%) agreed. The symptomatic group in PRISM-EZ comprised 232 patients (47.7% of those in the symptomatic arm that completed PRISM) whereas the intensive group comprised 270 subjects (53.5% of those in the intensive arm that completed PRISM). In total, 191 subjects in the symptomatic group (82.3%) and 213 subjects in the intensive group (78.8%) completed the study, providing 613 patient-years of follow up in the symptomatic group and 698 patient years of follow up in the intensive group. Relevant demographic and clinical characteristics of the study population at the baseline visit of PRISM-EZ are shown in table 4.1. Prior to entering PRISM-EZ, participants had been followed up for an average of 4.3 years since enrolment in PRISM giving a total duration of 7.3 years follow up. The groups were well matched for most variables at entry to PRISM-EZ with the exception of serum total adjusted ALP concentrations which were lower at baseline in the intensive treatment group and bisphosphonate use which was more common in the intensive group.

Figure 4.1: Disposition of Study Subjects



Disposition of the patients from the start of PRISM to the end of PRISM-EZ is shown. 'Withdrawn' indicates that the patient was withdrawn by the clinician, 'declined' indicates that the patient declined further follow up and 'lost' indicates that the patient was lost to follow up.

Table 4.1: Baseline characteristics and standardised mean differences between the groups unadjusted and adjusted IPTW

	Intensive (n=270)	Symptomatic (n=232)	Standardized mean difference unadjusted	Standardized mean difference adjusted
Male	149(55.2)	125(53.9)	0.026	-0.008
Age at entry to PRISM (years)	270; 71.2±8.1	232; 71.8±8.2	-0.066	-0.006
Age at entry to PRISM-EZ (years)	270; 75.6±8.1	232; 76.0±8.2	-0.058	-0.006
Duration of treatment in PRISM	270; 4.3±0.8	232; 4.3±0.8	0.020	0.001
Age at diagnosis of PDB (years)	268; 63.4±10.2	232; 63.8±10.4	-0.038	-0.011
Family history	45(16.7)	43(18.5)	-0.049	-0.007
Affected bones				
Skull	66(24.4)	62(26.7)	-0.052	0.001
Spine	104(38.5)	82(35.3)	0.066	0.005
Pelvis	181(67.0)	142(61.2)	0.122	0.015
Femur	98(36.3)	71(30.6)	0.121	-0.001
Tibia	53(19.6)	42(18.1)	0.039	-0.001
Other	96(35.6)	78(33.6)	0.041	-0.005
Deafness	46(17.0)	38(16.4)	0.018	0.003
Serum creatinine	261; 92.0±24.9	220; 94.6±30.1	-0.093	0.015
Bone pain	166(61.5)	149(64.2)	-0.057	0.004
Bone deformity	134(49.6)	108(46.6)	0.062	0.006
Previous fractures	121(44.8)	103(44.4)	0.008	0.012
Previous orthopaedic surgery for Paget's disease	70(25.9)	48(20.7)	0.124	0.009
SF36 sub scales				
Physical Functioning	220; 36.2±13.0	189; 36.4±12.5	-0.018	-0.040
Role Physical	215; 38.5±12.1	187; 40.1±12.2	-0.130	-0.080

Bodily Pain	216; 41.5±11.4	188; 41.9±11.7	-0.033	-0.031
General Health	216; 41.6±10.6	186; 43.7±10.8	-0.202	-0.104
Vitality	215; 44.6±11.3	187; 45.5±11.6	-0.084	-0.085
Social Functioning	214; 42.4±12.7	183; 43.3±13.9	-0.071	-0.040
Role Emotional	213; 40.8±14.7	186; 42.1±14.5	-0.090	-0.033
Mental Health	213; 48.1±11.0	186; 49.7±11.0	-0.149	-0.107
SF36 summary scales				
Physical Component Summary	208; 37.5±11.5	180; 38.3±11.6	-0.068	-0.050
Mental Component Summary	208; 47.3±11.8	180; 48.9±12.3	-0.132	-0.075
Arthritis-Specific Health Index	208; 37.3±13.3	180; 38.2±13.5	-0.066	-0.048
EuroQol (EQ-5D)				
EQ-5D	212; 0.634±0.290	179; 0.62±0.32	0.053	0.009
Stanford health assessment questionnaire				
Standard Disability Index	212; 0.932±0.836	184; 0.92±0.81	0.011	-0.001
Alternative Disability Index	212; 0.740±0.779	184; 0.70±0.72	0.054	0.003

Significant discrepancies were noted in baseline characteristics prior to adjustment. Values are mean ± standard deviation or numbers (%), SMD-standardised mean difference. Arthritis specific health index (ASHI) is an arthritis-specific version of the SF36, and scores were calculated from the SF36 data on a range of 0 (poorest health) to 100 (best health) and were not normalised. Each domain of the SF36 is scored from 0 (poorest health) to 100 (best health) and normalised to a mean of 50-scores greater than 50 indicating better quality of life and scores less than 50 indicating reduced quality of life. The physical and mental component summary scores were derived

from these (SF36) domain scores. The health assessment questionnaire (HAQ) assesses the extent of functional ability according to a four-point scale from no disability (0) to serious disability (3). Scores for the HAQ were calculated without the assistance of aids and devices (standard HAQ) and with the assistance of aids and devices (alternative HAQ). EQ-5D measures general health status in 5 dimensions resulting in a score of between 1 (full health) and 0 (death).

4.3.2 Treatment Received

There was a significant difference between the two groups in the range and type of bisphosphonates given for PDB during the study, which was consistent with the study protocol (Table 4.2). Zoledronate was given to a higher proportion of patients in the intensive group (28.1% vs 10.3%, $p<0.001$) whereas fewer patients in the intensive group received pamidronate (4.8% vs 15.5%, $p<0.001$). The proportion of patients who received risedronate and etidronate was similar in both treatment groups. Some patients also were receiving bisphosphonate treatment for osteoporosis (alendronate 70mg weekly, risedronate 35mg weekly; and ibandronate 150mg monthly or 3mg intravenously 3 monthly) but there was no significant difference in the proportion of patients who received these medications between the groups. Analgesics and NSAID were used by a high proportion of patients in both treatment groups with no significant differences between the groups (Table 4.3).

Table 4.2: Bisphosphonate treatment during study

	Intensive (n=270)	**Symptomatic (n=232)**
Any Bisphosphonate treatment	127(47.0)	91 (39.2)
Bisphosphonates for PDB		
Risedronate	18 (6.7)	14 (6.0)
Etidronate	3 (1.1)	2 (0.9)
Tiludronate	2 (0.7)	5 (2.2)
Pamidronate	15 (5.6)	37 (15.9)**
Clodronate	1 (0.4)	0 (0)
Zoledronate	87(32.2)	27 (11.6)***
Bisphosphonates for osteoporosis		
Alendronate	16 (5.9)	8 (3.4)
Oral ibandronate	2 (0.7)	1 (0.4)
Intravenous ibandronate	0 (0)	1 (0.4)*
Risedronate	10 (3.7)	5 (2.2)

Values are numbers (%) of patients who received bisphosphonate treatment for PDB or osteoporosis. Differences between groups: **, p=0.002, *** p<0.001.

Table 4.3: Analgesic use during study

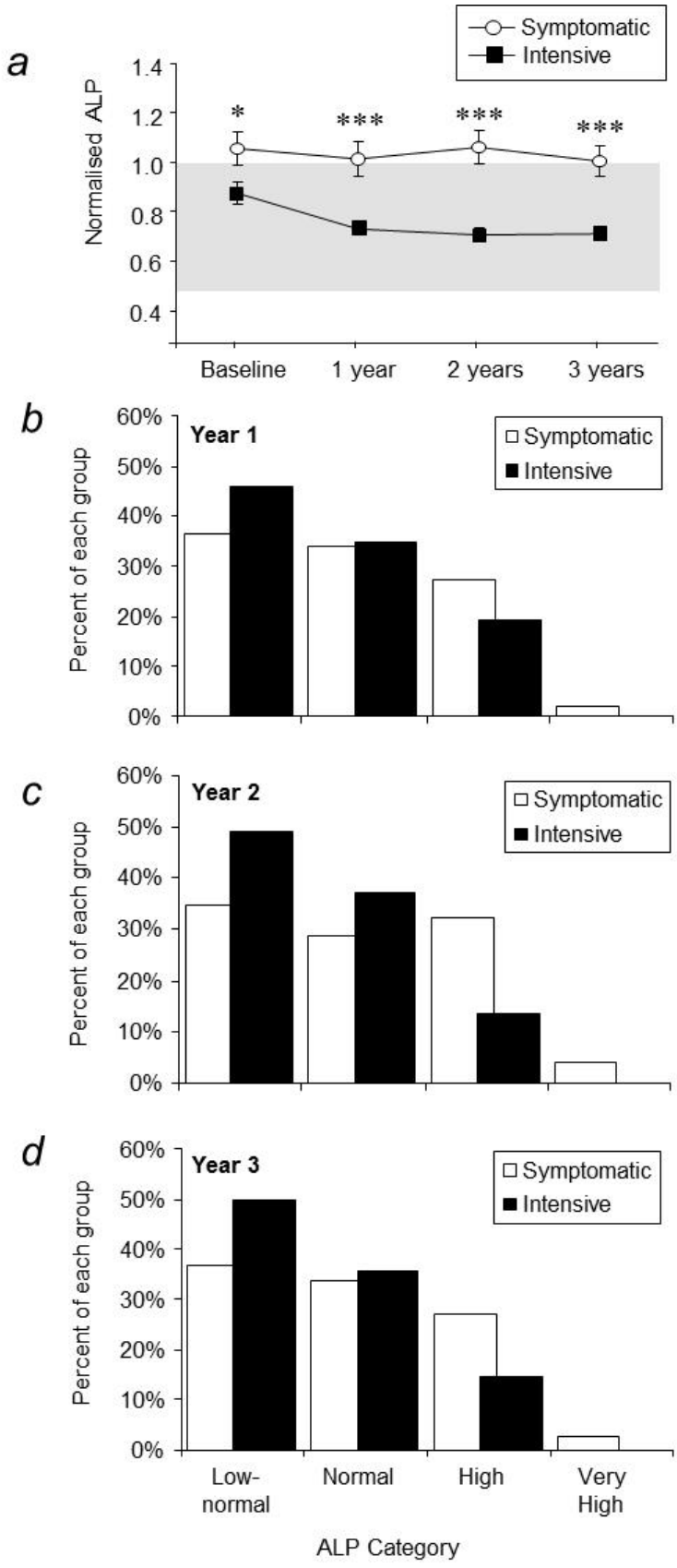
	Intensive (n=270)	**Symptomatic (n=232)**	**Hazard ratio [95% CI]**
Any analgesic	200 (74.1)	182 (78.4)	0.94 [0.85-1.04]
Paracetamol	122 (45.2)	120 (51.7)	0.87 [0.72-1.05]
Compound analgesics	87 (32.2)	64 (27.6)	1.18 [0.89-1.57]
Dihydrocodeine or Tramadol	33 (12.2)	33 (14.2)	0.92 [0.58-0.48]
Anti-neuropathic drugs	3 (1.1)	5 (2.2)	0.40 [0.09-1.72]
Opioids	12 (4.4)	11 (4.7)	0.89 [0.39-2.05]
NSAID	70 (25.9)	64 (27.6)	0.97 [0.72-1.30]

Values are numbers (%) of patients who received analgesics during the study

4.3.3 Serum ALP

Serum concentrations of ALP during the study and the proportions of patients with ALP in the low normal, normal, high and very high ranges are shown in figure 4.2. The methodology used in obtaining normalised ALP levels are as described in Section 4.2.3 in the 'Methods' section of this chapter. The ALP values were lower in the intensive group at baseline and the differences increased during the study. For example, at baseline 75.1% of the intensive group and 63.8% of the symptomatic group had normal or low ALP concentrations (p=0.018) but by year two ALP values were normal or low normal in 86% of the intensive group compared with 63.8% of the symptomatic group (p<0.0001). Corresponding values at year 3 were 69.8% and 83.9% (p<0.0001).

Figure 4.2: Serum ALP concentrations



Changes in adjusted ALP during the study are shown in panel a. The symbols are means and vertical bars standard error of the mean. The reference range is indicated by the shaded area. Panels b, c and d show the proportion of patients with serum ALP values in each category in years 1-3. Low normal: at or below the 50th centile of the normal range; Normal: between the 50th centile and the upper limit of normal; High: up to three times normal; very high: more than three times normal.

4.3.4 Quality of Life and Bone Pain

Quality of life summary scores assessed by the SF36 questionnaire are shown in table 4.4. There was no sustained difference in quality of life measures in favour of one group or the other during the study. Changes in physical component summary score (+1.6, p=0.04) and arthritis specific health index (+2.7, p<0.001) were observed at year 1 in favour of the intensive treatment group whereas changes in the mental component summary score at year three favoured the symptomatic treatment group (-2.4, p=0.019). Changes in the Stanford disability index favoured the symptomatic group at year 1 (-0.06, p=0.05). There was no significant difference in EQ5D scores between treatment groups (data not shown). Changes in the SF36 subscales are shown in table 4.5. Differences in role physical (+1.7, p=0.04) and bodily pain (+2.8, p<0.001) were observed which favoured the intensive group at one year but not at other time points. The magnitude of change in SF36 scores was in all cases less than the five-point threshold, which is considered clinically significant [130]. The proportion of patients with bone pain was not different between groups during the study, but for bone pain rated by the physician as being due to PDB there was a marginal benefit at year two in favour of the intensive group (+1.3, p=0.009).

Table 4.4: Quality of life summary scores and bone pain

	Time	Intensive (n=270)	Symptomatic (n=232)	SMD [95% CI]	p-value
Physical component summary	Year 1	185, 37.5±0.9	153, 37.0±0.9	1.6 [0.1,3.1]	0.04
	Year 2	136, 36.1±1.0	120, 36.9±1.1	0.8 [-1.5, 3.2]	0.49
	Year 3	172, 36.4±0.9	160, 35.6±0.9	0.9 [-1.1, 2.9]	0.39
ASHI	Year 1	185, 37.6±1.0	153, 36.4±1.0	2.7 [1.3, 4.0]	<0.001
	Year 2	136, 35.7±1.2	120, 36.6±1.2	0.7 [-1.6, 2.9]	0.57
	Year 3	172, 36.6±1.0	160, 36.1±1.0	0.8 [-1.4, 3.1]	0.46
Mental component summary	Year 1	185, 46.9±0.9	153, 47.6±1.0	0.6 [-1.2, 2.4]	0.54
	Year 2	136, 46.6±1.0	120, 48.2±1,0	-0.2 [-2.2, 1.9]	0.88
	Year 3	172, 46.7±0.9	160, 49.0±1.0	-2.4 [-4.3, -0.4]	0.02
Standard disability index	Year 1	185, 0.92±0.06	153, 1.02±0.6	-0.06 [-0.13, 0.00]	0.05
	Year 2	136, 1.05±0.07	120, 1.03±0.6	-0.03 [-0.17, 0.12]	0.71
	Year 3	172, 1.09±0.07	160, 1.15±0.7	0.04 [-0.10, 0.19]	0.56
Alternative disability index	Year 1	185, 0.72±0.06	153, 0.76±0.06	0.00 [-0.06, 0.07]	0.99
	Year 2	136, 0.84±0.07	120, 0.80±0.07	-0.03 [-0.15, 0.08]	0.57
	Year 3	172, 0.86±0.06	160, 0.87±0.06	0.04 [-0.09, 0.17]	0.57
Bone pain	Year 1	148 (54.8)	115 (49.6)	0.52 [-0.5, 1.5]	0.29
	Year 2	123 (45.6)	104 (44.8)	0.02 [-0.6, 0.7]	0.94
	Year 3	130 (48.1)	112 (48.3)	0.68 [-0.1, 1.5]	0.09
Pagetic bone pain	Year 1	44 (16.3)	40 (17.2)	-0.57 [-1.7, -.6]	0.34
	Year 2	40 (14.8)	36 (15.5)	1.30 [0.3, 2.3]	0.009
	Year 3	34 (12.6)	37 (15.9)	-0.71 [-2.0, 0.5]	0.26

Values are numbers of patients, numbers of patients (%) and mean ± standard deviation; SMD-standardised mean difference. ASHI-Arthritis specific health index;

Table 4.5: Effect of treatment on SF-36 subdomains

	Time	Intensive (n=270)	Symptomatic (n=232)	SMD [95% CI]	p-value
Physical Function	Year 1	191, 36.1±1.0	168, 36.1±0.9	0.2 [-1.5, 1.8]	0.86
	Year 2	143, 34.9±1.1	126, 34.6±1.1	1.2 [-0.4, 2.8]	0.13
	Year 3	177, 35.5±1.0	167, 34.6±1.0	0.4 [-1.5, 2.2]	0.68
Role Physical	Year 1	192, 37.8±0.9	166, 37.6±0.9	1.7 [0.0, 3.3]	0.049
	Year 2	140, 37.3±1.0	124, 38.0±1.1	1.0 [-1.0, 3.0]	0.34
	Year 3	177, 37.8±0.9	164, 36.8±0.9	1.1 [-1.4, 3.5]	0.39
Bodily Pain	Year 1	191, 41.8±0.8	167, 40.0±0.8	2.8 [1.3, 4.2]	<0.001
	Year 2	142, 40.1±1.0	127, 40.5±1.0	0.4 [-2.2, 2.9]	0.77
	Year 3	177, 41.1±0.9	166, 40.8±0.9	0.6 [-1.6, 2.7]	0.61
General Health	Year 1	190, 41.3±0.8	162, 42.0±0.8	0.5 [-1.4, 2.5]	0.60
	Year 2	140, 40.9±1.0	124, 42.7±1.0	1.2 [-1.6, 3.9]	0.41
	Year 3	176, 40.1±0.8	165, 41.3±0.8	-1.2 [-3.4, 0.9]	0.26
Vitality	Year 1	190, 44.4±0.8	166, 44.1±0.9	1.2 [-0.7, 3.1]	0.20
	Year 2	139, 43.5±0.9	127, 44.6±1.0	-0.5 [-2.5, 1.5]	0.62
	Year 3	176, 44.2±0.8	165, 44.9±0.9	-1.4 [-3.6, 0.8]	0.22
Social Functioning	Year 1	191, 42.2±0.9	162, 42.3±1.0	0.3 [-1.4, 2.0]	0.70
	Year 2	139, 41.2±1.1	122, 42.3±1.1	-0.3 [-3.1, 2.5]	0.84
	Year 3	174, 40.6±1.0	165, 42.2±1.0	-1.7 [-4.2, 0.8]	0.18
Role Emotional	Year 1	190, 40.3±1.1	165, 40.0±1.1	1.1 [-1.0, 3.2]	0.31
	Year 2	142, 40.1±1.3	125, 40.0±1.3	1.2 [-1.8, 4.2]	0.43
	Year 3	176, 40.4±1.1	161, 41.4±1.2	-1.1 [-3.7, 1.5]	0.40
Mental health	Year 1	191, 48.0±0.8	166, 48.8±0.9	0.8 [-0.8, 2.3]	0.33
	Year 2	139, 47.3±0.9	126, 49.2±0.9	-0.6 [-2.6, 1.3]	0.53
	Year 3	176, 47.9±0.8	165, 49.3±0.9	-0.8 [-3.2, 1.5]	0.48

Values are numbers of patients and mean ± standard deviation; SMD-standardised mean difference.

4.3.5 Skeletal Events

Data on fractures and orthopaedic procedures are summarised in table 4.6. Fractures were (non-significantly) more common in the intensive group 22 *vs.* 12, adjusted hazard ratio 1.90, 95% confidence intervals 0.91- 3.98, p=0.087 as were orthopaedic procedures 15 vs 8, adjusted hazard ratio 1.53 [0.63-3.72], p=0.356. Most events occurred in unaffected bone but a similar trend was observed for fractures and orthopaedic procedures in bone that was affected by PDB. A time to event analysis showed that when fractures and orthopaedic procedures were analysed as a composite endpoint these were significantly more common in the intensive group (adjusted hazard ratio 1.93 95% CI 1.05-3.55, p = 0.034), although it should be noted that this was a post-hoc analysis that was not pre-specified in the study protocol, that combining entirely different outcome measures is not conventional and that the total numbers of events used to generate this finding was low.

Table 4.6: Fractures and Orthopaedic Procedures

	Intensive (n=270)	**Symptomatic (n=232)**	**Hazard ratio [95% CI]**	**p-value**
Patients with fracture or orthopaedic surgery	34 (12.6)	17 (7.3)	1.93 [1.05-3.55]	0.034
Patients with fracture and orthopaedic surgery	3	3		
Number of fractures and orthopaedic procedures	40	22		
Patients with fracture	22 (8.1)	12 (5.2)	1.90 [0.91-3.98]	0.087
Number of fractures	24	12		
Fractures in Pagetic	5	2		

bone				
Patients requiring orthopaedic surgery	15 (5.6)	8 (3.4)	1.53 [0.63-3.72]	0.356
Number of procedures	16	10		
Procedures in Pagetic bone	7	4		
Joint replacements	11	4		
Osteotomy	2	2		
Other procedures	1	3		

Comparison between groups is adjusted for IPTW. The hazard ratio and p-values are for time to first event.

4.3.6 Exposure to Bisphosphonates and Skeletal Events

Since both treatment groups received bisphosphonates during the study, an exploratory analysis was conducted to evaluate possible associations between bisphosphonate use during PRISM-EZ and skeletal events. The results for fracture are shown in table 4.7 and for orthopaedic procedures in table 4.8. While there was no clear association between treatment with individual bisphosphonates and skeletal events, there was an association between bisphosphonate treatment and fractures. Fractures were more common in patients that received bisphosphonates in the intensive group (12.7% vs. 3.1%, p=0.004), the symptomatic group (12.8% vs. 0%, p<0.0001) and both groups combined (12.8% vs.1.5%, p<0.0001). The vast majority of these fractures however did not involve Pagetic bone. For orthopaedic surgery there was no significant excess of procedures in patients that received bisphosphonates as compared with those that did not in the intensive group (4.0% vs. 7.6%, p=0.20), the symptomatic group (6.1% vs. 1.5%, p=0.06) or both groups combined (4.8% vs. 4.4%, p=0.81)

Table 4.7: Bisphosphonate treatment and fractures

	Intensive			Symptomatic		
Fracture	Yes	No	(%)	Yes	No	(%)
Zoledronate	9	78	10.3%	3	24	11.1%
Risedronate	1	17	5.6%	1	13	7.1%
Pamidronate	4	11	26.7%	4	33	10.8%
Etidronate	1	2	33.3%	1	1	50%
Tiludronate	1	1	50%	0	5	0%
Alendronate	2	14	12.5%	2	6	25%
Ibandronate	0	0	0%	1	0	100%
Any bisphosphonate	18	123	12.7%	12	82	12.8%
No bisphosphonate	4	125	3.1%	0	138	0%

The number and percentages of patients exposed to individual bisphosphonates that experienced a fracture in each treatment arm are shown, as well as summary data for numbers and percentages with exposure to any bisphosphonate and those who did not receive bisphosphonates. Data on patients who had received any bisphosphonate were analysed in 141 patients in the Intensive treatment group and 94 patients in the Symptomatic treatment group, where the occurrence of fracture (or not) was recorded. Data on patients who were not treated with bisphosphonate were

analysed in 129 patients in the Intensive treatment group and 138 in the Symptomatic treatment group, where the occurrence of fracture (or not) was recorded.

Table 4.8: Bisphosphonate treatment and orthopaedic procedures

	Intensive			Symptomatic		
Orthopaedic Surgery	Yes	No	(%)	Yes	No	(%)
Zoledronate	4	83	4.6%	3	24	11.1%
Risedronate	0	28	0%	0	19	0%
Pamidronate	1	14	6.7%	2	35	5.4%
Etidronate	0	3	0%	1	1	50%
Tiludronate	0	2	0%	0	5	0%
Alendronate	1	15	6.3%	0	8	0%
Ibandronate	0	0	0%	0	1	0%
Any bisphosphonate	6	145	4%	6	93	6.1%
No bisphosphonate	9	110	7.6%	2	131	1.5%

The number and percentages of patients exposed to individual bisphosphonates that underwent orthopaedic surgery in each treatment arm are shown, as well as

summary data for numbers and percentages with exposure to any bisphosphonates and those who did not receive bisphosphonates. Data on patients who had received any bisphosphonate were analysed in 151 patients in the Intensive treatment group and 99 patients in the Symptomatic treatment group, where the requirement for orthopaedic surgery (or not) was recorded. Data on patients who were not treated with bisphosphonate were analysed in 119 patients in the Intensive treatment group and 133 in the Symptomatic treatment group, where the requirement for orthopaedic surgery (or not) was recorded.

4.3.7 Adverse Events

Adverse events reported during the study are summarised in table 4.9. Serious adverse events were (non-significantly) more frequent in the intensive group at 32.2% compared with 28.4% of the symptomatic group (relative risk 1.28, 95% CI 0.96-1.42]. The proportion of patients with non-serious adverse events was almost identical in both groups (relative risk 0.99, 95% CI [0.92-1.08]. Some rare adverse events that have previously been associated with bisphosphonates were also more common in the intensive group including osteonecrosis of the jaw (1 *vs.* 0) uveitis (1 *vs.* 0) and arrhythmias (14 vs. 5) and delayed fracture healing (2 *vs.* 1)

Table 4.9: Adverse events reported during study

	Intensive (n=270)	**Symptomatic (n=232)**	**Relative risk [95% CI]**
Serious Adverse Events	87 (32.2)	66 (28.4)	1.28 [0.96-1.72]
Total Number of Adverse Events	226 (83.7)	196 (84.5)	0.99 [0.92-1.08]
Cardiovascular	67 (24.8)	49 (21.1)	1.080 [0.76-1.52]
Cerebrovascular	4 (1.5)	3 (1.3)	1.027 [0.20-5.18]
CNS	28 (10.4)	28 (12.1)	0.918 [0.54-1.56]
Endocrine	28 (10.4)	21 (9.1)	1.628 [0.92-2.87]
ENT	28 (10.4)	26 (11.2)	1.020 [0.59-1.75]
Gastrointestinal	54 (20.0)	46 (19.8)	1.014 [0.69-1.48]
Genitourinary and renal	41 (15.2)	39 (16.8)	1.024 [0.67-1.57]
Haematological	10 (3.7)	9 (3.9)	1.081 [0.43-2.71]
Musculoskeletal	123 (45.6)	104 (44.8)	1.063 [0.86-1.31]
Miscellaneous	33 (12.2)	32 (13.8)	0.993 [0.61-1.62]
Respiratory	48 (17.8)	43 (18.5)	0.911 [0.61-1.35]
Ophthalmic	34 (12.6)	41 (17.7)	0.685 [0.44-1.07]
Skin	41 (15.2)	33 (14.2)	1.108 [0.70-1.74]

Values are number (%) of people with at least one event.

4.4 Discussion

The aim of the PRISM-EZ study was to determine whether long-term suppression of bone turnover with intensive bisphosphonate therapy conferred any clinical advantage over routine care in patients with established PDB. [3] The rationale for the study stemmed from previous suggestions that normalisation of bone turnover might improve clinical outcome in PDB by preventing complications. [40, 138] Indeed the treatment strategy employed in the intensive group was very similar to that advised in the recent Endocrine Society guidelines which suggested that most patients with PDB should be treated with potent bisphosphonates with the aim of lowering biochemical markers of bone turnover to within the lower half of the normal range. [40]

On entry to PRISM-EZ, participants had already been treated with intensive or symptomatic therapy for an average of 4.3 years, which when added to treatment given during the extension, provided a total duration of treatment and follow up of about 7.3 years. As expected, serum ALP concentrations were significantly lower in the intensive group at baseline and the differences between groups increased as the study progressed. Despite the fact that bone turnover was suppressed to a significantly greater extent in the intensive group there were no consistent differences in quality of life, bodily pain or bone pain between the two treatment groups. There were statistically significant differences at year one in bodily pain, physical component summary score and arthritis specific health index favouring the intensive group but the effect size was below the threshold that is considered clinically significant. Bone pain rated by the physician as being due to PDB was slightly less common at year two in the intensive group but again, the magnitude of effect was small and the difference was not observed at other time-points. In deriving this result, it is acknowledged that there will have been inter-observer bias in interpreting bone pain thought due to PDB. The pain data are consistent with the

observations of Reid and colleagues who reported that zoledronate treatment improved SF36 bodily pain score by a margin of about two points when compared with risedronate. [130] However the data from the present study, like those of Reid demonstrate that while zoledronate may have a slightly greater effect on pain, the effect size is small and at least in the present study, was not sustained. It is also important to emphasise that the statistical analysis of quality of life data was not adjusted for multiple testing and some of the differences may have arisen by chance.Intensive treatment was associated with an increased number of fractures and orthopaedic procedures as well as an increased number of serious adverse events including one case of osteonecrosis of the jaw. In view of the fact that bisphosphonates were given to both groups, an exploratory analysis was conducted to determine if the excess of skeletal events might have been explained by exposure to individual bisphosphonates. This analysis did not show an association with bisphosphonate type and fractures or orthopaedic procedures but did reveal that fractures occurred more commonly in patients that received bisphosphonates in both treatment groups. While the overall number of fractures and orthopaedic procedures was small, the observations raise the possibility that prolonged intensive bisphosphonate therapy of PDB may increase the risk of fracture due to oversupression of bone turnover, although none of the fractures in the present study met the American Society for Bone and Mineral Research (ASBMR) criteria for atypical femoral fractures. [147]

An important strength of PRISM-EZ study is that it is the only randomised trial to examine the long-term effects of management on the clinical outcome and complications of PDB in a routine care setting. While the participants were elderly and many had suffered complications of PDB such as deafness, fractures and bone deformity this is the typical profile of patients who are being treated in secondary care in the UK and internationally. [25] The results are therefore likely to be generalisable to patients being treated in secondary care in the UK and beyond. It is important to recognise that the same may not apply to treatment naïve patients or

those with early disease who might gain benefit from suppression of metabolic activity.

The results of PRISM-EZ have implications for clinical practice in light of the recent recommendations made by the Endocrine Society guideline group [40] which suggested that potent bisphosphonates should be prescribed in most patients with PDB with the aim of reducing bone turnover markers below the midpoint of the reference range and preventing complications. The results of the PRISM-EZ study indicate that in patients with established disease, this strategy confers no clinical benefit over using bisphosphonates on a symptomatic basis and raises the possibility that it may be harmful. It can be concluded therefore that in elderly patients with PDB the focus should be on treating the patient rather than the ALP concentration.

Chapter 5

The Usefulness of ALP in Predicting Clinical Response to Bisphosphonate Therapy in PDB

Abstract

Serum concentration of ALP is widely used as a marker of metabolic activity in PDB and as a measure of efficacy of bisphosphonate treatment. It is widely believed that a reduction in ALP should in theory correspond with an improvement in the clinical features and complications typically associated with this condition. There is however little information on the correlation between ALP concentrations and bone pain which is the most common complication of PDB. In this chapter an analysis was conducted to study the relation between serum total ALP concentrations and pain in patients with PDB in the PRISM study.

At baseline, significantly more patients with a normal or low serum total ALP had previously used a bisphosphonate and the participating physician judged more patients with a high or very high serum total ALP to have PDB related bone pain. At 1 year, more patients with a normal or low ALP had been randomised in to the 'intensive' treatment arm of PRISM and more patients with a high or very high serum total ALP had been randomised in to the 'symptomatic' arm.

No difference was seen between changes in patient and physician reported bone pain with changes in serum ALP and changes in SF36 scores. A binary logistic regression analysis performed to assess for any determinants of improvement revealed no particular factors which significantly influenced improvement of patient and physician reported bone pain

In summary, this study has demonstrated that changes in serum total ALP do not correlate well with changes in patient and physician reported bone pain.

5.1 Introduction

The diagnosis of PDB is often made based on a combination of an elevated serum ALP together with positive findings on bone scintigraphy usually with the clinical features typical of this condition.[3] Serum ALP is also normally used to monitor for response to bisphosphonate treatment and disease relapse.[3] Serum ALP as a marker of bone formation is a test which is widely available and relatively cheap to analyse as compared to other markers of bone formation including P1NP or markers of bone resorption including serum or urine C-terminal telopeptide (CTx) or NTx.[29, 30] Bisphosphonate therapy, due to its inhibitory effects on both bone osteoclast and osteoblast activity has been demonstrated to reduce the circulating markers of bone resorption and formation in patients with PDB. Many experts postulate that normalisation or reduction in ALP with bisphosphonate therapy should theoretically lead to an improvement in the symptoms associated with PDB in addition to a higher likelihood of preventing the occurrence of complications since an elevated ALP is a sign of increased metabolic and hence disease activity.[40] The PRISM study [36] and its extension PRISM-EZ [133] however disputes this theory by demonstrating no significant difference in terms of clinical outcomes between active normalisation of serum ALP with repeated courses of bisphosphonates versus a strategy of managing symptoms with analgesia initially followed by bisphosphonate therapy in non-responders to analgesia. Serum ALP throughout PRISM [36] and PRISM-EZ [133] was consistently and significant lower in patients randomised to intensive bisphosphonate therapy. The PRISM-EZ trial [133] (described in chapter 4 of this thesis) in fact also reported that patients who received intensive bisphosphonate therapy have a higher risk of fracture or require orthopaedic surgery highlighting the possible danger of over-suppression of bone cellular activity.

In this chapter a subset of patients who were recruited in to the PRISM trial was analysed [36] to determine if serum ALP is a useful marker in predicting response of bone pain and SF36 scores following treatment with bisphosphonate therapy.

5.2Methods

5.2.1 Patients

The randomisation process of participants of the PRISM trial has previously been described. [36] Out of the 1324 patients who were assigned to treatment, a total of 454 patients at baseline were identified for analysis based on the fact that information on SF36 scores, the presence or absence of patient and physician reported bone pain and ALP was available in these subjects. Information on these subjects was collected at baseline and repeated after 12 months.

5.2.2 Variables Assessed

Information collected at baseline included gender, age at baseline and at diagnosis, previous number of bisphosphonates received prior to baseline, use of bisphosphonate in the preceding 12 months prior to baseline, number of bones affected, patient reported bone pain and bone pain reported by the physician as being caused by PDB (physician reported bone pain). It has previously been demonstrated that physicians use the following characteristics to determine whether bone pain is caused by PDB; pain located at an affected site that has previously responded to bisphosphonate therapy, pain at rest and pain at night. [36] Information was also collected on SF36 scores (all domains), use of analgesia and serum total ALP concentrations.

The ALP concentrations were normalised to the upper limit of the local laboratories' reference range to give adjusted ALP values. Using this notation an adjusted ALP concentration of 1.0 is equivalent to a value at the upper limit of the reference range.

Serum concentrations of ALP were further categorised into low (<50% of normal range), normal (50-100% of normal range), high (100-300% of normal range) and very high (>300% of normal range) subgroups. Changes in ALP concentrations between baseline and 12 months were recorded in terms of absolute change as a continuous variable but also categorised into 'stable' (no change in category), 'increased' (increased by one or more categories) or 'reduced' (decreased by one or more categories). At 12 months these assessments were repeated but additional information was collected on analgesia use, bisphosphonate therapy and treatment allocation (symptomatic or intensive)

Change in SF36 scores between 12 months and baseline were calculated and analysed as a continuous variable with a positive value indicating improvement at 12 months and a negative value indicating deterioration at 12 months.

Change in bone pain at 12 months compared to baseline was recorded as either 'no pain at baseline, no pain at 12 months', no pain at baseline, pain at 12 months', 'pain at baseline, improved at 12 months' and 'pain at baseline, pain still present at 12 months'.

5.2.3 Statistical Analyses

Between group differences at baseline and 12 months were analysed using the one-way Analysis of Variance (ANOVA) for continuous variables and cross-tabulation with chi-Square testfor categorical variables. Significance between individual groups was calculated using the Dunnett's post-hoc test, setting ALP 'low' as the reference for comparison between the other categories of ALP (normal, high and very high). [148]

Dunnett's post-hoc test is a multiple comparison test comparing each of a number of factors with a single control by interval estimation or hypothesis testing when sampling from a distribution where the normality assumption is reasonable. [148] It is acknowledged that multiple testing carries a risk of false positive findings and hence a p value of <0.05 represents nominal significance. [148]

The change in pain scores at 12 months compared to baseline were evaluated using ANOVA. Change in pain at 12 months compared to baseline was compared with ALP category (low, normal, high, very high) using cross-tabulation with chi-square. Change in pain versus change in SF36 scores was analysed using ANOVA. A binary logistic regression analysis was used to analyse the determinants of improvement in bone pain at 12 months compared to baseline

5.3 Results

5.3.1 Baseline Clinical and Demographic Data in Relation to ALP Levels

The clinical characteristics of patients at the baseline visit are illustrated in table 5.1, based on the serum concentrations of ALP. As expected, prior use of bisphosphonates was more common in patients with normal or low ALP at baseline but there was not a difference between individual subcategories of bisphosphonate. There was no difference between the ALP groups and patient reported bone pain, but bone pain reported by the physician was less frequent in the low normal ALP and low ALP groups compared with the high ALP group. None of the other characteristics differed between ALP groups.

Table 5.1: Patient characteristics at baseline according to ALP category

	Very High ALP (n=21)	**High ALP (n=176)**	**Normal ALP (n=128)**	**Low ALP (n=129)**	**P value**
Age at Baseline	74.67 ± 8.33	71.14 ± 8.76	72.48 ± 7.05	71.27 ± 7.37	0.1405
Age diagnosed	67.62 ± 11.52	63.51 ± 9.81	65.05 ± 9.81	62.51 ± 10.46	0.0671
Males	16 (76.2%)	97 (55.1%)	68 (53.1%)	69 (53.5%)	0.2496
Prior use of bisphosphonate	5 (23.8%)	43 (24.4%)	49 (38.3%)	49 (38.0%)	0.0214
Presence of bone pain judged by patient	14 (66.7%)	127 (72.2%)	81 (63.3%)	95 (73.6%)	0.2563
Presence of bone pain judged by physician	10 (47.6%)	100 (56.8%)	51 (39.8%)	57 (44.2%)	0.0218
SF36 Bodily Pain	42.57 ± 8.95	42.61 ± 10.95	40.94 ± 10.15	39.42 ± 10.65	0.0689
SF36 Physical Summary	36.83 ± 10.10	38.30 ± 11.77	37.83 ± 10.20	36.26 ± 11.71	0.4942
SF36 Mental Summary	51.54 ± 10.07	49.61 ± 11.43	48.01 ± 10.50	49.24 ± 11.66	0.5083
Baseline analgesia					
Paracetamol	14 (66.7%)	124 (70.5%)	77 (60.2%)	77 (59.7%)	0.1640
NSAID	12 (57.1%)	122 (69.3%)	84 (65.6%)	87 (67.4%)	0.6895
Other	18 (85.7%)	138 (78.4%)	94 (73.4%)	86 (66.7%)	0.0750

Values are mean ± SD or number (%). The p-values shown are from Chi square tests for categorical variables and ANOVA for continuous variables. For continuous variables, Dunnett's post-hoc test using the low ALP group as reference revealed no difference between groups.

5.3.2 Clinical and Demographic Data in Relation to ALP Levels at 12 Months

The clinical characteristics of patients at the 12 month follow up visit are illustrated in table 5.2, based on the serum concentrations of ALP. The only significant difference between groups was with respect to treatment allocation where about 60% of patients allocated to intensive bisphosphonate treatment had normal or low serum total ALP concentrations as compared with 30% where ALP levels were high and 16.7% where ALP levels were very high ($p<0.0001$). Conversely, significantly more patients with a high (69.1%) or very high (83.3%) ALP at 1 year were found to have been randomised in to the symptomatic treatment arm of the study. None of the other characteristics differed between ALP groups.

Table 5.2: Patient Characteristics at Year 1 according to ALP Category

	Very High ALP (n=6)	**High ALP (n=94)**	**Normal ALP (n=149)**	**Low ALP (n=188)**	**P Value**
Intensive treatment arm	1 (16.7%)	29 (30.9%)	91 (61.1%)	114 (60.6%)	<0.0001
Symptomatic treatment arm	5 (83.3%)	65 (69.1%)	58 (38.9%)	74 (39.4%)	<0.0001
Presence of pain judged by patient	3 (50.0%)	59 (62.8%)	88 (59.1%)	116 (61.7%)	0.8734
Presence of pain judged by physician	2 (33.3%)	35 (37.2%)	41 (27.5%)	56 (29.8%)	0.4418
SF36 Bodily Pain	49.58 ± 9.66	42.68 ± 11.25	40.37 ± 10.73	40.96 ± 11.08	0.1212
SF36 Physical Summary	43.09 ± 9.19	38.72 ± 11.92	37.72 ± 11.74	37.33 ± 11.18	0.6138
SF36 Mental Summary	57.18 ± 8.25	47.95 ± 12.24	48.98 ± 10.22	48.27 ± 11.46	0.3258
Use of Analgesia at 1 Year					
Paracetamol	2 (33.3%)	62 (66.0%)	105 (70.5%)	122 (64.9%)	0.2356
NSAID	1 (16.7%)	30 (31.9%)	50 (33.6%)	65 (34.6%)	0.8093
Other	6 (100%)	71 (75.5%)	108 (72.5%)	135 (71.8%)	0.4431
Use of Bisphosphonate in Year 1	1 (16.7%)	48 (51.1%)	75 (50.3%)	106 (56.4%)	0.2051

Values are mean ± SD or number (%). The p-values shown are from Chi square tests for categorical variables and ANOVA for continuous variables. For continuous variables, Dunnett's post-hoc test using the low ALP group as reference revealed no difference between groups.

5.3.3 Relation Between Change in ALP and Patient and Physician Reported Bone Pain

In order to investigate the relation between changes in bone turnover and the changes in bone pain, a comparison was made between change in ALP and adjusted ALP and changes in patient and physician reported bone pain between baseline and at year 1 (Tables 5.3 and 5.4). This showed that there was no significant difference in the mean change total ALP concentrations or adjusted ALP concentrations and patient as well as physician reported bone pain.

Table 5.3: Change in ALP compared with change in patient reported bone pain

	No pain at Baseline. No pain at 12 months (n=71)	**No pain at Baseline. Pain at 12 months (n=43)**	**Pain at Baseline. Improved at 12 months (n=75)**	**Pain at Baseline. Pain still present at 12 months (n=222)**	**P value**
Change in ALP	-43.6 ± 124.1	-34.0 ± 89.3	-42.5 ± 119.5	-39.1 ± 117.9	0.973
Change in Adjusted ALP	-0.31 ± 0.83	-0.26 ± 0.66	-0.27 ± 0.80	-0.30 ± 0.99	0.988

Values are mean ± SD or number (%). There was no significant difference between the groups

Table 5.4: Change in ALP compared with change in physician reported bone pain

	No pain at Baseline. No pain at 12 months (n=17)	**No pain at Baseline. Pain at 12 months (n=19)**	**Pain at Baseline. Improved at 12 months (n=36)**	**Pain at Baseline. Pain still present at 12 months (n=84)**	**P value**
Change in ALP	-23.2 ± 54.7	-4.6 ± 40.3	-58.1 ± 117.45	-44.1 ± 140.3	0.4112
Change in Adjusted ALP	-0.20 ± 0.46	-0.03 ± 0.34	-0.41 ± 0.90	-0.37 ± 1.24	0.5138

Values are mean ± SD or number (%). There was no significant difference between the groups

5.3.4 Relation Between Patient and Physician Reported Bone Pain and Quality of Life Assessed by SF36

The relation between changes in patient and physician reported bone pain and changes in quality of life assessed by the SF36 score are shown in tables 5.5 and 5.6

Table 5.5: Change in SF36 scores compared with change in patient reported bone pain

	No pain at Baseline. No pain at 12 months (n=63)	**No pain at Baseline. Pain at 12 months (n=40)**	**Pain at Baseline. Improved at 12 months (n=69)**	**Pain at Baseline. Pain still present at 12 months (n=202)**	**P value**
Change in SF36 Physical Function	+0.15 ± 5.6	-0.88 ± 7.4	-0.20 ± 6.9	+0.81 ± 7.3	0.4608
Change in SF36 Role Physical	+0.44 ± 7.5	-1.74 ± 9.8	-1.01 ± 8.4	+0.07 ± 9.4	0.5284
Change in SF36 Bodily Pain	+1.15 ± 6.8	-1.78 ± 8.19	-0.30 ± 6.4	+0.56 ± 7.3	0.1761
Change in SF36 General Health	+1.85 ± 6.4	+0.11 ± 8.5	+2.12 ± 10.3	+0.86 ± 8.7	0.5639
Change in SF36 Vitality	+1.40 ± 9.8	-0.75 ± 8.7	+0.18 ± 7.3	-0.07 ± 8.0	0.5600
Change in SF36 Social Functioning	+0.87 ± 7.9	-2.32 ± 13.2	+2.75 ± 11.6	+1.07 ± 9.7	0.1006
Change in SF36 Role Emotional	-2.22 ± 9.9	-2.62 ± 13.5	-0.31 ± 11.4	-0.79 ± 13.5	0.6857
Change in SF36 Mental Health	+1.90 ± 8.0	-2.24 ± 8.5	+0.56 ± 8.7	+0.21 ± 8.8	0.1277
Change in SF36 Physical Summary	+1.04 ± 5.8	-1.04 ± 5.8	-0.46 ± 5.5	+0.40 ± 5.4	0.1982
Change in SF36 Mental Summary	+0.14 ± 8.4	-2.42 ± 10.4	+0.98 ± 8.1	-0.44 ± 8.0	0.2246

Values are mean ± SD or number (%), p value < 0.05 considered significant

Table 5.6: Change in SF36 scores compared with change in physician reported bone pain

	No pain at Baseline. No pain at 12 months(n=17)	**No pain at Baseline. Pain at 12 months (n=16)**	**Pain at Baseline. Improved at 12 months(n=32)**	**Pain at Baseline. Pain still present at 12 months(n=74)**	**P value**
Change in SF36 Physical Function	-2.21 ± 10.8	+2.46 ± 4.3	+1.66 ± 6.1	+1.04 ± 6.0	0.1719
Change in SF36 Role Physical	+2.91 ± 13.0	+3.20 ± 11.3	-0.41 ± 7.4	+0.57 ± 7.8	0.4427
Change in SF36 Bodily Pain	+1.09 ± 5.2	+2.85 ± 11.1	+2.84 ± 5.8	-0.62 ± 6.1	0.0550
Change in SF36 General Health	+3.03 ± 11.9	+1.16 ± 13.0	-0.80 ± 6.9	+1.46 ± 8.7	0.5423
Change in SF36 Vitality	+1.10 ± 6.5	-0.72 ± 9.2	-1.24 ± 7.4	+0.84 ± 8.0	0.5710
Change in SF36 Social Functioning	+3.53 ± 5.8	+2.53 ± 15.9	-0.51 ± 5.2	+1.40 ± 10.8	0.5502
Change in SF36 Role Emotional	-5.26 ± 13.5	+1.70 ± 9.7	+3.52 ± 15.6	-1.08 ± 11.4	0.1047
Change in SF36 Mental Health	+0.50 ± 8.3	-1.72 ± 10.0	-0.81 ± 6.2	-0.07 ± 10.0	0.8821
Change in SF36 Physical Summary	-0.31 ± 5.4	+0.13 ± 3.8	+0.49 ± 5.7	+0.91 ± 5.4	0.8272
Change in SF36 Mental Summary	-0.81 ± 7.4	-0.26 ± 8.0	+0.10 ± 7.6	-0.22 ± 8.8	0.9877

Values are mean ± SD or number (%), p value < 0.05 considered significant

5.3.5 Predictors of Improvement in Patient Reported Bone Pain

In order to identify predictors of improvement in patient reported bone pain a binary logistic regression analysis was conducted entering relevant baseline variables into the model. The results are shown in Table 5.7. This showed that there were no particular factors which significantly improved patient reported bone pain

Table 5.7: Determinants of improvement in patient-reported bone pain at 12 months

	OR (95% CI)	P Value
Age at Baseline	0.88 (0.75-1.04)	0.0770
Age Diagnosed	1.05 (0.89-1.24)	0.4960
Patient reported bone pain at baseline	1.86 (0.33-10.40)	0.4977
SF36 Bodily Pain Score at Baseline	1.02 (0.94-1.11)	0.6534
SF36 Physical Summary at Baseline	1.03 (0.96-1.12)	0.3992
SF36 Mental Summary at Baseline	0.94 (0.89-1.00)	0.0633
Randomised to intensive treatment arm	1.67 (0.30-9.26)	0.5500
Received bisphosphonates in 1st year of PRISM	0.78 (0.14-4.34)	0.7756
Change in Adjusted ALP between baseline and 12 months	0.21 (0.01-2.86)	0.2320
Male	1.98 (0.36-11.03)	0.4200
Deformity at baseline	0.74 (0.13-4.09)	0.7220
Previous Fracture in Pagetic Bone	2.14 (0.24-19.11)	0.5310
Previous Orthopaedic Surgery	0.99 (0.11-8.73)	0.9970
Previous use of Bisphosphonate	2.61 (0.51-13.21)	0.2560

p value < 0.05 considered significant

5.3.6 Predictors of Improvement in Physician Reported Bone Pain

In order to identify predictors of improvement in physician reported bone pain thought to be due to PDB, a binary logistic regression analysis was conducted entering relevant variables into the model. The results are shown in Table 5.8. This showed that there were no particular factors which significantly improved physician reported bone pain

Table 5.8: Determinants of improvement in physician reported bone pain at 12 months

	OR (95% CI)	P Value
Age at Baseline	0.98 (0.92-1.03)	0.4040
Age Diagnosed	1.02 (0.97-1.08)	0.3700
Physician reported bone pain at baseline	0.11 (0.03-0.38)	0.2018
SF36 Bodily Pain Score at Baseline	0.98 (0.95-1.02)	0.4352
SF36 Physical Summary at Baseline	0.99 (0.96-1.03)	0.8756
SF36 Mental Summary at Baseline	0.98 (0.95-1.01)	0.2480
Randomised to intensive treatment arm	0.72 (0.36-1.43)	0.3443
Received bisphosphonates in 1st year of PRISM	0.97 (0.47-1.98)	0.9330
Change in Adjusted ALP between baseline and 12 months	0.87 (0.33-2.29)	0.7800
Male	0.85 (0.43-1.70)	0.6480
Deformity at baseline	0.63 (0.30-1.32)	0.2160
Previous Fracture in Pagetic Bone	0.54 (0.12-2.43)	0.3920
Previous Orthopaedic Surgery	0.94 (0.37-2.41)	0.8930
Previous use of Bisphosphonate	1.62 (0.78-3.34)	0.2010

p value < 0.05 considered significant

5.4 Discussion

Serum total ALP concentration is widely used as a biomarker of disease activity in PDB and as a marker of treatment response. Although pain is the most common presenting symptom in PDB [25] there is little information on the relationship between serum total ALP levels and bone pain. The aim of this analysis sought to determine if serum concentrations of total ALP correlated with the presence of bone pain at the baseline visit in PRISM participants and also to determine if changes in ALP following 12 months of therapy were associated with an improvement in bone pain.

As expected patients with either a normal or low ALP at baseline were significantly more likely to have used bisphosphonates before entry into the PRISM study. There was an association between baseline ALP and physician reported bone pain at baseline since fewer patients had bone pain in the groups with low ALP and normal ALP. However there was no difference in patient reported bone pain or SF36 physical or mental summary scores or SF36 bodily pain in relation to ALP concentrations at baseline (Table 5.1). The data also demonstrated however, that ALP concentrations are not associated with a significant impact on overall bodily pain or quality of life. This is presumably because pain in PDB can occur not only as the result of increased metabolic activity but also as the result of complications such as secondary osteoarthritis and nerve compression syndromes.

At year 1, patients randomised in to the 'intensive' arm of PRISM were more likely to have either a normal or low ALP and this finding was statistically significant. No significant difference was seen in terms of improvement of pain or SF36 scores or use of analgesia. No correlation was seen between change in pain and change in ALP levels between baseline and 1 year. Similarly no correlation was seen between change in pain and change in SF36 scores (bodily pain, mental and physical summary) between baseline and 1 year. No factors were found to be significant

determinants of improvement in patient and physician reported pain from the binary logistic regression analysis. This demonstrates that reductions in ALP do not correlate well with response of pain in PDB which suggests that in many patients, pain may be due to complications of the disease rather than increased metabolic activity (see below).

A limitation of this study was the measurement of the presence or absence of pain as a categorical variable (yes/no) with a high risk of inter-observer bias and variation in patient and physician reported bone pain. The author acknowledges that the use of a continuous variable as a measurement of pain, for example with the use of a visual analogue score may have reduced this bias and would have provided a more accurate quantification of the severity of any pain which may have been present.

Previous studies comparing the effect of alendronate [76] and tiludronate [132] versus etidronate have found no significant difference in terms of improvement in bone pain between bisphosphonates despite a significant decrease in ALP after alendronate and tiludronate therapy. A further study analysing the effect of risedronate versus etidronate showed a statistically significant improvement in bone pain from baseline with the risedronate group (with a corresponding statistically significant decrease in ALP) but no difference between groups in terms of the SF36 questionnaire. [75] In a study of zoledronate versus risedronate, the SF36 physical summary showed a small improvement at 6 months until 54 months and SF36 bodily pain scores were improved at 24 and 36 months with zoledronate. [35, 130] More patients in the zoledronate group had reduced or normalised ALP after treatment compared with patients randomised to receive risedronate. [35, 130]

A previous study analysing the effect of tiludronate on markers of bone turnover and its relation with PDB disease as reflected by change in appearance in bone scintigraphy revealed that P1NP and bone specific ALP (bAP) were the bone formation markers most closely linked with PDB disease activity post tiludronate treatment. [149] This study did not look at whether or not change in P1NP and bAP correlated with an improvement in bone pain or SF36 scores. [149] A recent

systematic review in to bone turnover markers in PDB suggests that P1NP is the most sensitive and specific marker in monitoring PDB disease activity (by way of bone scintigraphy) outperforming total ALP, bAP and urine NTx. [30]

The reasons for the lack of association between changes in ALP and changes in bone pain in the present study can only be speculated upon. Although it has been hypothesised that pain experienced by patients with PDB is often multifactorial, the actual mechanism causing pain in the context of PDB is in fact poorly understood. In addition to the other types of bone formation markers described, it may also be that markers of bone resorption may correlate better with changes in bone pain and this could be a future avenue of study. Some of the newer cytokines such as RANK-L and MCSF may also play a role in determining one's response to treatment and could potentially correlate better with any improvement in bone pain, although this association has yet to be assessed.

In summary, this study has shown that although serum ALP was more likely to be suppressed in patients randomised to the intensive treatment group, no significant improvement in SF36 scores and bone pain judged by either the patient or physician was seen in patients whose ALP had normalised or remained normal at Year 1 compared with baseline.

Chapter 6

Conclusions and Future Directions

Conclusions and future directions

This MD has demonstrated that the majority of patients with PDB do not actually come to medical attention. Of those that do, bone pain has been demonstrated to be the commonest presenting complaint. Unfortunately complications associated with PDB including fracture, deformity and deafness continue to frequently present both at diagnosis and despite bisphosphonate treatment, causing significant morbidity in our patients.

Despite being the second commonest metabolic bone disease, there continues to be many areas of uncertainty with regards to the optimal treatment strategy in patients diagnosed with PDB. The systematic review undertaken across studies examining the effect of bisphosphonate on PDB has demonstrated a higher number of patients reporting an improvement in bone pain with bisphosphonate treatment compared with placebo. The PRISM and PRISM-EZ studies however has shown no difference in terms of clinical outcomes between an intensive treatment strategy with bisphosphonates aimed at normalising ALP and a symptomatic approach to treatment using primarily analgesia. [36, 133] Zoledronate is currently the most commonly used bisphosphonate for this condition and is highly effective in suppressing bone turnover. Its repeated use has been shown however to be associated with a non-significant increased incidence of clinical fracture, or for the requirement for orthopaedic surgery in PRISM and PRISM-EZ. [36, 133] Although statistical significance (in support of a higher rate of events in the intensive arm) was obtained in PRISM-EZ when both these outcomes were combined, it is acknowledged that this composite outcome was not a pre-specified outcome measure, that combining entirely different outcome measures is not conventional and that the total numbers of events used to generate this finding was low. Caution should hence be applied when interpreting the significance of this result.

The measurement of serum ALP in monitoring the effects of bisphosphonate treatment and disease activity has been shown to poorly correlate with changes in bone pain and SF36 scores after treatment is administered. This biomarker however continues to be widely used due to its low cost and availability. Unfortunately the use of biomarkers such as bAP and P1NP, although previously shown to be more sensitive and specific then ALP in its correlation with PDB disease activity, remains limited primarily due to the high monetary costs associated with performing these tests.

One exciting prospect for the future lies with the ZiPP study, which is currently underway and will examine PDB in an altogether different aspect, namely the prevention of the occurrence of symptoms and complications associated with this disease by treating asymptomatic relatives of patients known to have PDB. [115] Another future avenue of study might be to develop drugs which specifically target proteins involved in mediating osteoclast overactivity, although the therapeutic effects of such drugs may not be as profound as with Zoledronate since multiple, rather than a solitary defect gives rise to the pagetic osteoclast.

In summary, although this MD has provided an in-depth analysis in to the clinical presentation, effects of bisphosphonate treatment and the usefulness of serum ALP in predicting clinical response to treatment, many challenges remain to be overcome, including identifying the best strategy to reduce or prevent the development of complications associated with PDB, the optimal treatment strategy in patients who present with symptoms and the reduction in cost of assays of biomarkers such as bAP and P1NP in order to increase its availability and affordability; before even better outcomes for patients with PDB may be achieved.

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